

Copper(I)-Catalysed Reaction of Hydrazonyl Chlorides with Homopropargylic Alcohols: Regioselective Synthesis of 5-Substituted Pyrazoles

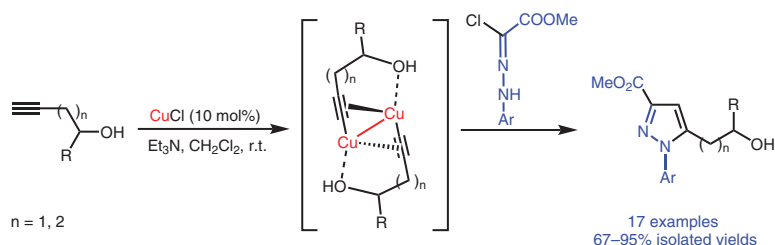
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In memory of Professor Geatano Zecchi. With admiration and
gratitude, G.M. remembers his depth of thinking and immense
knowledge of heterocyclic chemistry.



Received: 07.10.2022

Accepted after revision: 14.11.2022

Published online: 28.11.2022 (Version of Record)

DOI: 10.1055/s-0042-1751770; Art ID: SS-2022-10-0472-OP

Abstract Fully regioselective synthesis of 5-hydroxyethylpyrazoles was exploited by reacting hydrazonyl chlorides with homopropargylic alcohols in the presence of catalytic amounts of copper(I) chloride. Good yields of pyrazolic products and mild reaction conditions were experienced notwithstanding the known, poor reactivity of homopropargylic alcohols towards hydrazonyl chlorides. The role of copper(I) ion and some mechanistic insights for the formation of reaction products are also discussed.

Key words hydrazonyl chlorides, copper(I) catalysis, homopropargylic alcohols, pyrazoles, regioselective synthesis

The main feature of hydrazonyl halide chemistry relies upon their dehydrohalogenation, which occurs easily in the presence of a base.¹ The result of dehydrohalogenation leads to the in situ generation of the corresponding nitrilimine $\text{C}\equiv\text{N}^+-\text{N}^-$, an unstable and generally non-isolable dipolar intermediate.²

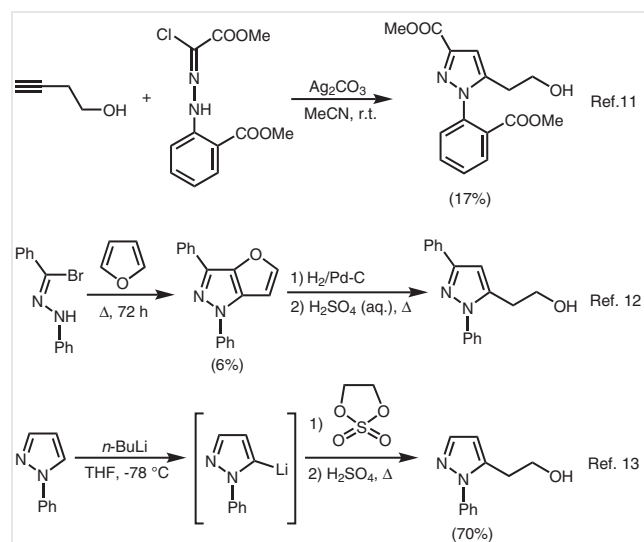
Nitrilimine 1,3-dipolar cycloaddition to the $\text{C}\equiv\text{C}$ bond represents one of the main methods for accessing the pyrazole ring³ but, unfortunately, this reaction very often gives mixtures of regioisomeric pyrazole cycloadducts.⁴ The poor regioselectivity of the reaction applies both to classical thermal cycloadditions according to Huisgen⁵ and to those conducted in the presence of metal cations in stoichiometric or catalytic mode, which have been introduced more recently.⁶

Clearly, the regioselective synthesis of the pyrazole ring from hydrazonyl chlorides in which the formation of the nitrilimine intermediate is avoided would be an important goal.

The limitation due to the lack of regioselectivity can be removed by reacting hydrazonyl chlorides in the presence of catalytic amounts of suitable copper(I) salts. This meth-

odology was recently developed by one of us⁷ and it allows pyrazole products to be obtained as single 5-substituted regioisomers. This is an undoubtedly synthetic advantage that is the consequence of the reaction mechanism, which is well described by a catalytic cycle involving metallate intermediates.^{7,8}

Beyond the mechanistic features of the copper(I)-catalysed reaction between hydrazonyl chlorides and terminal alkynes, the main interest in the synthesis of variously substituted pyrazoles lies in their pharmaco-clinical properties as analgesic, antifungal, anti-inflammatory, antibacterial, and antiviral agents.⁹ Not by chance, hydrazonyl halides have been defined as ‘a bubbling fountain of biologically active compounds’.¹⁰



Scheme 1 Literature approaches to 2-hydroxyethylpyrazoles (previous works)

The C=C bond of homopropargylic alcohols represents a problematic dipolarophile in the field of nitrilimine 1,3-dipolar cycloadditions (Scheme 1). In the presence of stoichiometric amounts of silver carbonate as the basic agent, the nitrilimine-alkyne reaction gave very low conversions to the desired 5-hydroxyethyl-substituted pyrazoles.¹¹ The meticulous study of this reaction revealed the loss of regioselectivity of the cycloaddition, which was also accompanied by the formation of a number of trivial by-products present in traces in the reaction mixture.¹¹

An indirect cycloadditive approach involving hydrazoneyl bromides required harsh conditions and the use of furan both as the dipolarophile and the solvent, followed by catalytic hydrogenation and acidic hydrolysis of the corresponding furopyrazole.¹²

In the face of these serious difficulties associated with the cycloadditive approach, it is not surprising that access to 5-hydroxyethylpyrazoles was pursued in a completely different way, that is, by direct lithiation of the pyrazole ring and subsequent reaction with ethylene sulfate.¹³

The present paper involves the study of the behaviour of homopropargyl alcohols **1a,b** towards hydrazoneyl chlo-

rides **2a–g** in the presence of catalytic amounts of copper(I) salts (Figure 1).

Optimisation of the reaction conditions was conducted by examining the behaviour of hydrazoneyl chloride **2a** towards 3-butyne-1-ol (**1a**) in the presence of a metal salt and an organic base. The results are shown in Table 1.

By way of comparison with reactions catalysed by metal salts, the first entry in Table 1 shows the nitrilimine-alkyne reaction pursued in the classical conditions, giving the novel pyrazole **3aa** and traces of its 4-(2-hydroxyethyl)-substituted isomer, not shown in the table, in a 9:1 ratio. Since

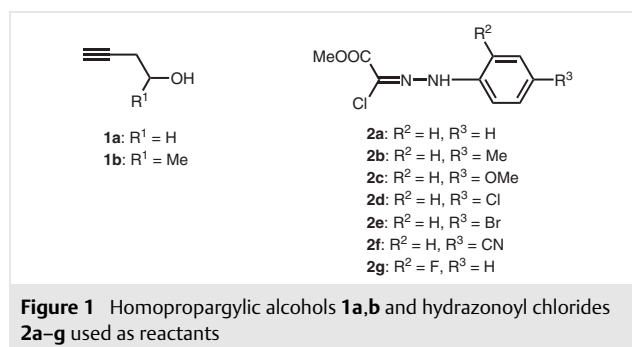


Table 1 Reaction between 3-Butyn-1-ol (**1a**) and Hydrazoneyl Chloride **2a**

| Entry | Metal salt (equiv.) | Base (equiv.) | Solvent | Temp (°C) | Time (h) | 3aa Yield (%) ^a |
|-------|-------------------------------------|-----------------------|---------------------------------|-----------|----------|-----------------------------------|
| 1 | – | Et ₃ N (5) | toluene | 100 | 4 | 17 |
| 2 | – | Et ₃ N (2) | toluene | 20 | 24 | – |
| 3 | Ag ₂ CO ₃ (2) | – | MeCN | 20 | 24 | <5 ^b |
| 4 | Ag ₂ CO ₃ (2) | – | MeCN | 80 | 4 | 17 |
| 5 | CuCl (0.1) | DBU (1) | CH ₂ Cl ₂ | 20 | 15 | 56 ^c |
| 6 | CuCl (0.1) | Et ₃ N (1) | toluene | 20 | 1.5 | 35 ^c |
| 7 | CuCl (0.1) | Et ₃ N (1) | DMF | 20 | 3 | 38 ^c |
| 8 | CuCl (0.1) | Et ₃ N (1) | MeCN | 20 | 18 | 65 ^c |
| 9 | CuCl (0.1) | Et ₃ N (1) | acetone | 20 | 18 | 37 ^c |
| 10 | CuCl (0.1) | Et ₃ N (1) | MTBE | 20 | 18 | 35 ^c |
| 11 | CuI (0.12) | Et ₃ N (1) | CH ₂ Cl ₂ | 20 | 18 | 55 ^c |
| 12 | Cu ₂ O (0.2) | Et ₃ N (1) | CH ₂ Cl ₂ | 20 | 18 | 60 ^c |
| 13 | CuOAc (0.1) | Et ₃ N (1) | CH ₂ Cl ₂ | 20 | 18 | 37 ^c |
| 14 | CuCl (0.05) | Et ₃ N (1) | CH ₂ Cl ₂ | 20 | 18 | 56 ^c |
| 15 | CuCl (0.1) | Et ₃ N (1) | CH ₂ Cl ₂ | 20 | 18 | 79 ^c |

^a Isolated yields after silica gel column chromatography.

^b Obtained with other unidentified by-products.

^c Obtained with variable amounts of diyne **4a** (5–35%).

the reaction between hydrazonoyl chloride **2a** and 3-buten-1-ol (**1a**) does not proceed after 24 hours at 20 °C (Table 1, entry 2), the generation of the nitrilimine intermediate under the same conditions for shorter reaction times can certainly be ruled out. From entry 3 of Table 1 it can be seen that, by stopping the reaction after 24 hours, the presence of silver salts in overstoichiometric amounts leads to the formation of small amounts of pyrazole **3aa**. This result appears *prima facie* rather surprising considering that silver carbonate is capable of increasing the reactivity of hydrazonoyl chlorides towards both ethylenic¹⁴ and allenic¹⁵ dipolarophiles.

Regardless of the different nature of the unsaturated carbon counterpart, the mentioned transformations usually require reaction times well in excess of 24 hours. This uncomfortable picture changes radically by conducting the reaction in the presence of catalytic amounts of copper(I) salts (Table 1, entries 5–15). As can be seen, the best results were obtained using copper(I) chloride at 10 mol% in dichloromethane at 20 °C (entry 15). The influence of the solvent is difficult to consider. Poor results are related to an increased presence of the diyne by-product **4a**, which is obtained both with solvents capable of exerting a complexing effect on the Cu⁺ cation (DMF, acetone) and with non-com-

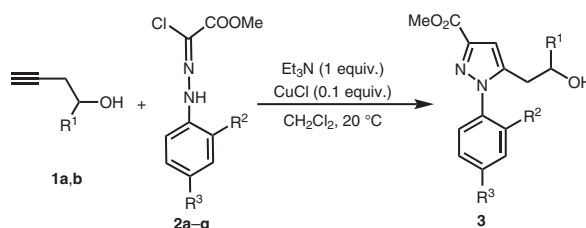
plexing solvents (toluene, MTBE). At this point, the optimised reaction conditions as shown in Table 1, entry 15, were extended to hydrazonoyl chlorides **2b–g** and homopropargyl alcohols **1a,b**.

All the reactions shown in Table 2 were completely regioselective, yielding pyrazoles **3** in 67–95% yields over 18–40 hours. Due to the presence of conjugated diynes **4** as by-products (5–15%, vide infra), isolation of pyrazoles **3** was pursued by chromatographic treatment on a silica gel column.

By-products **4** arise from the Glaser oxidative dimerisation of the alkynylcuprates originating from the corresponding homopropargyl alcohols.¹⁶ Since this side reaction competes with the nucleophilic addition of alkynylcuprate to the hydrazonoyl chloride, it proved impossible for us to suppress it. However, Glaser dimerisation was limited to 0–10% by conducting the reactions under nitrogen atmosphere (Scheme 2).

In order to gain some mechanistic insights about the reaction between homopropargyl alcohols **1** and hydrazonoyl chlorides **2** in the presence of copper(I) salts, it is necessary to consider the reaction between phenylacetylene and hydrazonoyl chloride **2a**. Under the same experimental conditions adopted for the homopropargyl alcohols, this latter

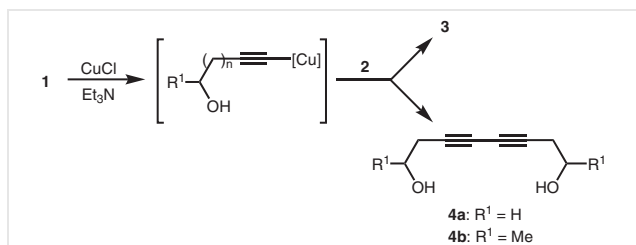
Table 2 Reaction between Homopropargylic Alcohols **1a,b** and Hydrazonoyl Chlorides **2a–g**



| Entry | 1 | R ¹ | 2 | R ² | R ³ | Pyrazole | Time (h) | Yield (%) ^{a,b} |
|-------|-----------|----------------|-----------|----------------|----------------|------------|----------|--------------------------|
| 1 | 1a | H | 2a | H | H | 3aa | 18 | 79 |
| 2 | 1a | H | 2b | H | Me | 3ab | 18 | 72 |
| 3 | 1a | H | 2c | H | OMe | 3ac | 19 | 81 |
| 4 | 1a | H | 2d | H | Cl | 3ad | 18 | 85 |
| 5 | 1a | H | 2e | H | Br | 3ae | 22 | 95 |
| 6 | 1a | H | 2f | H | CN | 3af | 26 | 83 |
| 7 | 1a | H | 2g | F | H | 3ag | 40 | 67 |
| 8 | 1b | Me | 2a | H | H | 3ba | 18 | 73 |
| 9 | 1b | Me | 2b | H | Me | 3bb | 18 | 77 |
| 10 | 1b | Me | 2c | H | OMe | 3bc | 18 | 69 |
| 11 | 1b | Me | 2d | H | Cl | 3bd | 18 | 81 |
| 12 | 1b | Me | 2e | H | Br | 3be | 18 | 88 |
| 13 | 1b | Me | 2f | H | CN | 3bf | 24 | 85 |
| 14 | 1b | Me | 2g | F | H | 3bg | 36 | 79 |

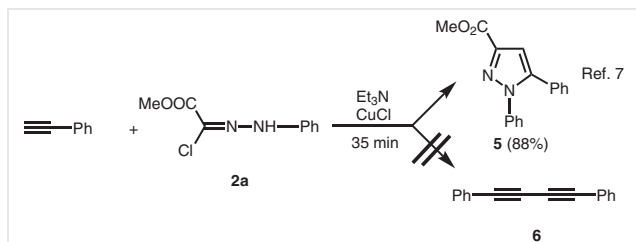
^a Isolated yields after silica gel column.

^b Obtained with variable amounts of diynes **4a,b**, which were separated by column chromatography (see Supporting Information).



Scheme 2 Competition between nucleophilic addition to hydrazone chlorides **2** and the Glaser dimerisation of homopropargylic alcohols **1**

reaction proceeds in only 35 minutes yielding pyrazole **5** in 88% yield (Scheme 3).⁷ The reaction time is thus very short compared to the analogous reaction with 3-butyne-1-ol. Furthermore, the diyne **6** was not formed as deduced from the ¹H NMR spectrum of the reaction crude.

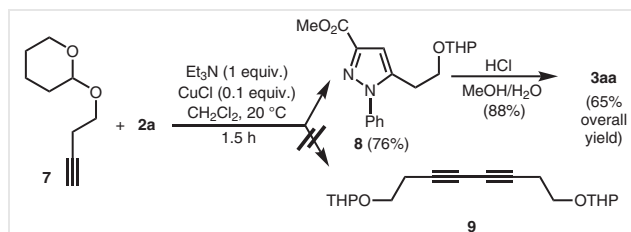


Scheme 3 Reaction between phenylacetylene and hydrazone chlorides **2a**⁷

Surprisingly, in the absence of hydrazone chloride, alcohol **1a** did not give the expected diyne **4a**, although on addition of copper(I) chloride the bright yellow colouration assumed by the reaction mixture indicates that copper(I) acetylide had been formed. Even after 24 hours, chromatographic analysis showed no presence of the diyne **4a**. Upon addition of a trace of hydrogen peroxide, however, its almost instantaneous and quantitative formation was realised, while the colour of the reaction mixture turned abruptly from bright yellow to dark green, suggesting a plausible change in the oxidation state of copper. By contrast, under the same reaction conditions the dimerisation of phenylacetylene is completed in 2 hours without the need to add hydrogen peroxide.

In a further experiment, the reaction between hydrazone chloride **2a** and tetrahydropyranyl ether **7**, prepared as described in the literature,¹⁷ was investigated. The behaviour of this transformation is quite similar to that observed in the case of phenylacetylene. In fact, pyrazole **8** was obtained in 90 minutes, and the corresponding by-product **9** was not detected (Scheme 4). By contrast, diyne **9** was easily obtained by reacting tetrahydropyranyl ether **7** in the absence of the hydrazone chloride.

The above experimental facts could be rationalized by considering the involvement of a 'ladderane' polymeric structure of the copper(I) phenylacetylide, known in the lit-



Scheme 4 Reaction between tetrahydropyranyl ether **7** and hydrazone chloride **2a**

erature since 2005 and obtained by powder diffraction experiments.¹⁸ However, the involvement of such a complex structure was considered implausible for reactions carried out in solvent, and the intermediacy of dinuclear complex **A** was proposed (Figure 2).¹⁹

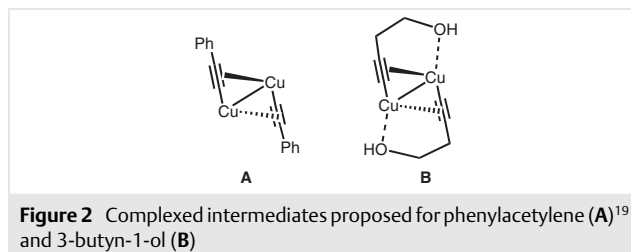


Figure 2 Complexed intermediates proposed for phenylacetylene (**A**)¹⁹ and 3-butyne-1-ol (**B**)

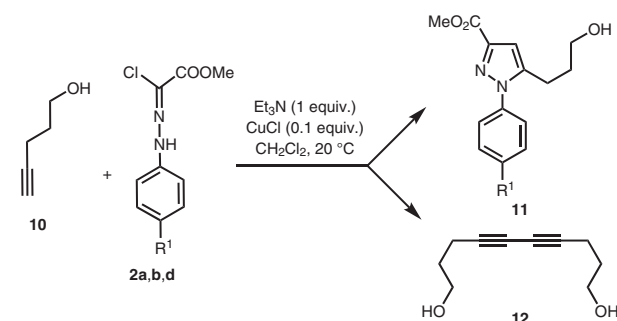
In the case of homopropargyl alcohols, intramolecular complexation of copper(I) by carbinol oxygen could be at work with the formation of intermediate **B** (Figure 2). The distorted tetrahedral geometry around the two copper(I) atoms is consistent with that exhibited by some binuclear copper(I) complexes.²⁰

Compared to the intermediate **A**, the involvement of the complexed one **B** is able to explain its lower reactivity towards: (i) the hydrazone chlorides, since alcohols **1** react much more slowly than phenylacetylene and, for such prolonged reaction times, the competing reaction of oxidative dimerisation emerges; (ii) the Glaser dimerisation to **4**, which for alcohols **1** occurs quickly only in the presence of traces of hydrogen peroxide as the oxidising agent.

If intramolecular complexation is prevented, as is the case of tetrahydropyranyl ether **7**, the intervention of an **A**-like intermediate can be assumed. Similar to what is observed for phenylacetylene, the reaction towards hydrazone chlorides is in fact rather fast and no diyne formation is observed.

In order to extend the applicability of the copper(I)-catalysed reaction between hydrazone chlorides and alkynols, the behaviour of 4-pentyne-1-ol (**10**) was considered. Pyrazoles **11** and diyne **12** by-products were obtained in comparable yield to homopropargyl alcohols **1** (Table 3).

As concluding remarks, the present synthetic approach to 5-hydroxyalkylpyrazole is superior to the nitrilimine-alkynol 1,3-dipolar cycloaddition despite the formation of

Table 3 Reaction between 4-Pentyn-1-ol (**10**) and Hydrazonoyl Chlorides **2a,b,d**

| Entry | 2 | R ¹ | Pyrazole | Time (h) | Yield (%) ^{a,b} |
|-------|-----------|----------------|------------|----------|--------------------------|
| 1 | 2a | H | 11a | 18 | 77 |
| 2 | 2b | Me | 11b | 18 | 80 |
| 3 | 2d | Cl | 11c | 19 | 83 |

^a Isolated yields after silica gel column.^b Obtained with variable amounts of the corresponding diyne **12** (4–8%, see experimental section).

conjugated diyne by-products. It also represents a viable alternative to the protocol based on the lithiation of the pre-formed pyrazole ring, since it does not require the use of low temperatures and hazardous reagents.

Furthermore, the three-step sequence involving the protection of the alkynol as a tetrahydropyranyl ether, the subsequent copper(I)-catalysed reaction and the release of the unprotected pyrazole **3aa** was also inferior in comparison with the direct alkynol-chlorohydrazone reaction. In fact, 5-hydroxyethyl-pyrazole **3aa** was obtained in 79% yield with the direct reaction and 65% in the three-step sequence.

Melting points were determined on a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded on a PerkinElmer 1725 X spectrophotometer. Mass spectra were determined on a VG-70EQ apparatus. ¹H NMR (400 MHz), ¹³C NMR (100 MHz), and ¹⁹F NMR (376 MHz) spectra were taken with a Bruker Avance instrument (in CDCl₃ solutions at r.t.). Chemical shifts are given as parts per million from TMS. Coupling constants (*J*) values are given in hertz (Hz) and are quoted to ± 0.1 Hz consistently with NMR machine accuracy. All solvents and reagents were purified by standard technique or used as supplied from chemical sources as appropriate. Reagent chemicals were purchased from Fluorochem Ltd. Solvents were dried and stored over 4 Å molecular sieves prior to use.

Hydrazonoyl chlorides **2a,c,d**,^{21a} **2b,e,f**,^{21b} **2g**,^{21c} and tetrahydropyranyl ether **7**¹⁷ were prepared according to literature procedures. Dienes **4a**,^{22a} **4b**,^{22b} **6**,^{22c} **12**,^{22d} and **9**^{22e} are known in the literature.

Optimisation procedures listed in Table 1, chromatographic *R_f* values of pyrazoles **3** and **11**, and the experimental details of diyne by-products **4** and **12** are provided in the Supporting Information.

Copper(I)-Catalysed Reaction between Acetylenic Alcohols **1a,b** and **10** and Hydrazonoyl Chlorides **2a–g**; General Procedure

To a clear, colourless solution of the appropriate acetylenic alcohol **1a,b**, or **10** (2.0 mmol) and Et₃N (0.20 g, 2.0 mmol) in anhyd CH₂Cl₂ (4 mL) was added CuCl (10 mg, 0.1 mmol) under vigorous magnetic stirring. A solution of the appropriate hydrazonoyl chloride **2** (2.0 mmol) in anhyd CH₂Cl₂ (4 mL) was added dropwise and the mixture was stirred at 20 °C for the time indicated in Table 2. The crude mixture was filtered over a Celite pad, which was washed with CH₂Cl₂ (3 × 5 mL). The solvent was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column with CH₂Cl₂/MeOH (95:5). Earlier fractions contained pyrazole products. Crystallisation of the eluate from *i*-Pr₂O gave the pure pyrazole **3** or **11**.

1-Phenyl-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (**3aa**)

Yield: 389 mg (79%); pale yellow solid; mp 110–112 °C.

IR (Nujol): 3450, 1735 cm^{−1}.

¹H NMR (400 MHz, CDCl₃): δ = 7.45–7.39 (m, 5 H, C₆H₅), 6.81 (s, 1 H, pyrazole-H4), 3.89 (s, 3 H, CO₂CH₃), 3.78 (t, *J* = 8.0 Hz, 2 H, CH₂OH), 2.85 (t, *J* = 8.0 Hz, 2 H, CH₂), 2.61 (br s, 1 H, OH).

¹³C NMR (100 MHz, CDCl₃): δ = 162.9 (s, CO₂CH₃), 143.3 (s, pyrazole-C3), 142.5 (s, C_q of Ph attached to pyrazole-N1), 138.6 (s, pyrazole-C5), 129.1–125.8 (d, CH_{arom}), 108.2 (d, pyrazole-C4), 60.4 (t, CH₂OH), 51.9 (q, CO₂CH₃), 29.1 (t, CH₂).

MS (EI): *m/z* = 246 [M⁺].

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₃H₁₄N₂O₃: 247.1083; found: 247.1060.

Anal. Calcd for C₁₃H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.44; H, 5.70; N, 11.43.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (**3ab**)

Yield: 374 mg (72%); pale yellow solid; mp 102–103 °C.

IR (Nujol): 3460, 1730 cm^{−1}.

¹H NMR (400 MHz, CDCl₃): δ = 7.31–7.25 (m, 4 H_{arom}), 6.82 (s, 1 H, pyrazole-H4), 3.92 (s, 3 H, CO₂CH₃), 3.80 (t, *J* = 8.0 Hz, 2 H, CH₂OH), 2.87 (t, *J* = 8.0 Hz, 2 H, CH₂), 2.41 (m, 4 H, overlapping of br s, 1 H, OH, and Ar-CH₃).

¹³C NMR (100 MHz, CDCl₃): δ = 162.9 (s, CO₂CH₃), 143.3 (s, pyrazole-C3), 142.3 (s, C_q of Ar attached to C-pyrazole-N1), 139.2 (s, pyrazole-C5), 136.3 (s, C_q of Ar-CH₃), 129.7 (d, CH_{arom}), 125.7 (d, CH_{arom}), 108.2 (d, pyrazole-C4), 60.8 (t, CH₂OH), 52.0 (q, CO₂CH₃), 29.3 (t, CH₂), 21.1 (q, Ar-CH₃).

MS (EI): *m/z* = 260 [M⁺].

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₄H₁₆N₂O₃: 261.1239; found: 261.1247.

Anal. Calcd for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.56; H, 6.17; N, 10.72.

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (**3ac**)

Yield: 447 mg (81%); white solid; mp 112–114 °C.

IR (Nujol): 3435, 1735, 1255 cm^{−1}.

¹H NMR (400 MHz, CDCl₃): δ = 7.35 (d, *J* = 8.0 Hz, 2 H_{arom}), 6.98 (d, *J* = 8.0 Hz, 2 H_{arom}), 6.84 (s, 1 H, pyrazole-H4), 3.93 (s, 3 H, CO₂CH₃), 3.86 (s, 3 H, OCH₃), 3.83 (t, *J* = 8.0 Hz, 2 H, CH₂OH), 2.86 (t, *J* = 8.0 Hz, 2 H, CH₂), 2.31 (br s, 1 H, OH).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.0 (s, CO_2CH_3), 159.9 (s, C_q , ArOCH_3), 143.2 (s, pyrazole-C3), 142.5 (s, C_q of Ar attached to pyrazole-N1), 131.7 (s, pyrazole-C5), 127.3 (d, CH_{arom}), 114.1 (d, CH_{arom}), 108.0 (d, pyrazole-C4), 60.6 (t, CH_2OH), 55.5 (q, OCH_3), 51.7 (q, CO_2CH_3), 29.3 (t, CH_2).

MS (EI): m/z = 276 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$: 277.1188; found: 277.1172.

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.82; H, 5.81; N, 10.10.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (3ad)

Yield: 476 mg (85%); pale yellow solid; mp 127–129 °C.

IR (Nujol): 3455, 1740 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.45–7.38 (m, 4 H_{arom}), 6.82 (s, 1 H, pyrazole-H4), 3.91 (s, 3 H, CO_2CH_3), 3.83 (t, J = 8.0 Hz, 2 H, CH_2OH), 2.86 (t, J = 8.0 Hz, 2 H, CH_2), 2.81 (br s, 1 H, OH).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.7 (s, CO_2CH_3), 143.6 (s, pyrazole-C3), 142.7 (s, C_q of Ar attached to pyrazole-N1), 137.1 (s, pyrazole-C5), 134.7 (s, C_q , ArCl), 129.3 (d, CH_{arom}), 127.1 (d, CH_{arom}), 108.4 (d, pyrazole-C4), 60.4 (t, CH_2OH), 52.0 (q, CO_2CH_3), 23.3 (t, CH_2).

MS (EI): m/z = 280 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$: 281.0693; found: 281.0707.

Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_3$: C, 55.62; H, 4.67; N, 9.98. Found: C, 54.59; H, 4.63; N, 10.11.

1-(4-Bromophenyl)-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (3ae)

Yield: 616 mg (95%); yellow solid; mp 109–113 °C.

IR (Nujol): 3455, 1735 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.80 (d, J = 8.2 Hz, 2 H_{arom}), 7.68 (d, J = 8.2 Hz, 2 H_{arom}), 6.88 (s, 1 H, pyrazole-H4), 3.93–3.90 (m, 5 H, overlapping of CO_2CH_3 and CH_2OH), 2.95 (t, J = 8.0 Hz, 2 H, CH_2), 2.32 (br s, 1 H, OH).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.7 (s, CO_2CH_3), 143.8 (s, pyrazole-C3), 142.6 (s, C_q of Ar attached to pyrazole-N1), 137.7 (s, pyrazole-C5), 132.2 (d, CH_{arom}), 127.4 (d, CH_{arom}), 122.8 (s, C_q , ArBr), 108.5 (d, pyrazole-C4), 60.8 (t, CH_2OH), 51.8 (q, CO_2CH_3), 29.2 (t, CH_2).

MS (EI): m/z = 324 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{BrN}_2\text{O}_3$: 325.0188; found: 325.0171.

Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}_3$: C, 48.02; H, 4.03; N, 8.62. Found: C, 47.98; H, 4.00; N, 8.66.

1-(4-Cyanophenyl)-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (3af)

Yield: 450 mg (83%); white solid; mp 131–135 °C.

IR (Nujol): 3440, 2230, 1735 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.82 (d, J = 8.0 Hz, 2 H_{arom}), 7.69 (d, J = 8.0 Hz, 2 H_{arom}), 6.90 (s, 1 H, pyrazole-H4), 3.94 (s, 3 H, CO_2CH_3), 3.91 (t, J = 8.0 Hz, 2 H, CH_2OH), 2.95 (t, J = 8.0 Hz, 2 H, CH_2), 2.82 (br s, 1 H, OH).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.5 (s, CO_2CH_3), 144.6 (s, pyrazole-C3), 143.0 (s, C_q of Ar attached to pyrazole-N1), 142.3 (s, pyrazole-C5), 133.1 (d, CH_{arom}), 126.2 (d, CH_{arom}), 117.7 (s, $\text{C}\equiv\text{N}$), 112.4 (s, C_q , ArCN), 109.2 (d, pyrazole-C4), 60.9 (t, CH_2OH), 52.1 (q, CO_2CH_3), 29.3 (t, CH_2).

MS (EI): m/z = 271 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_3$: 272.1035; found: 272.1019.

Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 62.03; H, 4.80; N, 15.44.

1-(2-Fluorophenyl)-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (3ag)

Yield: 354 mg (67%); colourless solid; mp 92–93 °C.

IR (Nujol): 3450, 1735, 1490 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.50–7.21 (m, 4 H_{arom}), 6.85 (s, 1 H, pyrazole-H4), 3.92 (s, 3 H, CO_2CH_3), 3.80 (m, 2 H, CH_2OH), 2.78 (t, J = 7.6 Hz, 2 H, CH_2), 2.22 (br s, 1 H, OH).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.7 (s, CO_2CH_3), 156.8 (d, $^1J_{\text{CF}}$ = 334 Hz, C_q , ArF), 144.4 (s, pyrazole-C3), 144.1 (s, pyrazole-C5), 131.4 (d, $^3J_{\text{CF}}$ = 10 Hz, CH_{arom}), 129.4 (d, CH_{arom}), 126.6 (s, $^2J_{\text{CF}}$ = 17 Hz, C_q of Ar attached to pyrazole-N1), 124.7 (d, $^3J_{\text{CF}}$ = 4 Hz, CH_{arom}), 116.5 (d, $^2J_{\text{CF}}$ = 26 Hz, CH_{arom}), 107.8 (d, pyrazole-C4), 60.2 (t, CH_2OH), 52.0 (q, CO_2CH_3), 28.8 (t, CH_2).

^{19}F NMR (376 MHz, CDCl_3): δ = -110.90.

MS (EI): m/z = 264 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{FN}_2\text{O}_3$: 265.0988; found: 265.0994.

Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}_3$: C, 59.09; H, 4.96; N, 10.60. Found: C, 59.05; H, 4.95; N, 10.64.

1-Phenyl-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3ba)

Yield: 380 mg (73%); white solid; mp 94–96 °C.

IR (Nujol): 3450, 1740, 1490 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.48–7.42 (m, 5 H, C_6H_5), 6.87 (s, 1 H, pyrazole-H4), 4.05–3.95 (m, 1 H, CHOH), 3.92 (s, 3 H, CO_2CH_3), 2.83–2.73 (m, 2 H, CH_2), 2.17 (br s, 1 H, OH) 1.17 [d, J = 7.5 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 163.0 (s, CO_2CH_3), 143.7 (s, pyrazole-C3), 142.5 (s, C_q of Ph attached to pyrazole-N1), 139.0 (s, pyrazole-C5), 129.2 (d, CH_{arom}), 129.0 (d, CH_{arom}), 126.2 (d, CH_{arom}), 108.8 (d, pyrazole-C4), 66.8 (d, CHOH), 52.0 (q, CO_2CH_3), 35.5 (t, CH_2), 23.1 [q, $\text{CH}(\text{OH})\text{CH}_3$].

MS (EI): m/z = 260 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_3$: 261.1239; found: 261.1245.

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.63; H, 6.20; N, 10.80.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3bb)

Yield: 422 mg (77%); white solid; mp 89–90 °C.

IR (Nujol): 3440, 1725 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.31 (d, J = 8.5 Hz, 2 H_{arom}), 7.26 (d, J = 8.5 Hz, 2 H_{arom}), 6.85 (s, 1 H, pyrazole-H4), 4.04–3.99 (m, 1 H, CHOH), 3.92 (s, 3 H, CO_2CH_3), 2.82–2.72 (m, 2 H, CH_2), 2.42 (s, 3 H, ArCH_3), 2.06 (br s, 1 H, OH) 1.17 [d, J = 5.0 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 163.0 (s, CO_2CH_3), 143.5 (s, pyrazole-C3), 142.5 (s, C_q of Ar attached to C-pyrazole-N1), 139.1 (s, pyrazole-C5), 136.5 (s, C_q , ArCH_3), 129.7 (d, CH_{arom}), 126.0 (d, CH_{arom}), 108.7 (d, pyrazole-C4), 66.8 (d, CHOH), 52.0 (q, CO_2CH_3), 35.5 (t, CH_2), 23.1 [q, $\text{CH}(\text{OH})\text{CH}_3$], 21.2 (q, ArCH_3).

MS (EI): m/z = 274 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3$: 275.1396; found: 275.1382.

Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.71; H, 6.64; N, 10.21.

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3bc)

Yield: 400 mg (69%); white solid; mp 99–102 °C.

IR (Nujol): 3440, 1725, 1255 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.36 (d, J = 8.2 Hz, 2 H_{arom}), 6.99 (d, J = 8.2 Hz, 2 H_{arom}), 6.87 (s, 1 H, pyrazole-H4), 4.08–4.00 (m, 1 H, CHOH), 3.95 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, OCH_3), 2.79–2.77 (m, 2 H, CH_2), 1.84 (br s, 1 H, OH) 1.21 [d, J = 5.2 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 163.0 (s, CO_2CH_3), 159.9 (s, C_q , ArOCH_3), 143.4 (s, pyrazole-C3), 142.5 (s, C_q of Ar attached to C-pyrazole-N1), 132.0 (s, pyrazole-C5), 127.6 (d, CH_{arom}), 114.3 (d, CH_{arom}), 108.5 (d, pyrazole-C4), 66.9 (d, CHOH), 55.6 (OCH_3), 52.0 (q, CO_2CH_3), 35.5 (t, CH_2), 23.1 [q, $\text{CH}(\text{OH})\text{CH}_3$].

MS (EI): m/z = 290 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_4$: 291.1345; found: 291.1353.

Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.09; H, 6.23; N, 9.68.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3bd)

Yield: 475 mg (81%); pale yellow solid; mp 116–118 °C.

IR (Nujol): 3435, 1740 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.42–7.37 (m, 4 H_{arom}), 6.81 (s, 1 H, pyrazole-H4), 4.03 (dd, J = 8.0, 5.2 Hz, 1 H, CHOH), 3.89 (s, 3 H, CO_2CH_3), 2.73 (d, J = 8.0 Hz, 2 H, CH_2), 2.46 (br s, 1 H, OH) 1.17 [d, J = 5.2 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 162.8 (s, CO_2CH_3), 143.8 (s, pyrazole-C3), 142.8 (s, C_q of Ar attached to pyrazole-N1), 137.4 (s, pyrazole-C5), 134.8 (s, C_q , ArCl), 129.4 (d, CH_{arom}), 127.4 (d, CH_{arom}), 109.0 (d, pyrazole-C4), 66.8 (d, CHOH), 52.1 (q, CO_2CH_3), 35.4 (t, CH_2), 23.2 [q, $\text{CH}(\text{OH})\text{CH}_3$].

MS (EI): m/z = 294 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{ClN}_2\text{O}_3$: 295.0849; found: 295.0833.

Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$: C, 57.05; H, 5.13; N, 9.50. Found: C, 57.09; H, 5.15; N, 9.56.

1-(4-Bromophenyl)-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3be)

Yield: 595 mg (88%); yellow solid; mp 121–123 °C.

IR (Nujol): 3440, 1730 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.61 (d, J = 8.2 Hz, 2 H_{arom}), 7.36 (d, J = 8.2 Hz, 2 H_{arom}), 6.86 (s, 1 H, pyrazole-H4), 4.03 (dd, J = 5.4, 5.0 Hz, 1 H, CHOH), 3.94 (s, 3 H, CO_2CH_3), 2.78 (d, J = 5.4 Hz, 2 H, CH_2), 2.16 (br s, 1 H, OH), 1.22 [d, J = 5.0 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 162.8 (s, CO_2CH_3), 144.0 (s, pyrazole-C3), 142.6 (s, C_q of Ar attached to C-pyrazole-N1), 138.0 (s, pyrazole-C5), 132.4 (d, CH_{arom}), 127.7 (d, CH_{arom}), 122.9 (s, C_q , ArBr), 109.0 (d, pyrazole-C4), 66.8 (d, CHOH), 52.1 (q, CO_2CH_3), 35.4 (t, CH_2), 23.3 [q, $\text{CH}(\text{OH})\text{CH}_3$].

MS (EI): m/z = 338 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{BrN}_2\text{O}_3$: 339.0344; found: 339.0331.

Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{BrN}_2\text{O}_3$: C, 49.57; H, 4.46; N, 8.26. Found: C, 50.01; H, 4.44; N, 8.29.

1-(4-Cyanophenyl)-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3bf)

Yield: 485 mg (85%); pale yellow solid; mp 136–139 °C.

IR (Nujol): 3440, 2225, 1730 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.79 (d, J = 8.0 Hz, 2 H_{arom}), 7.69 (d, J = 8.0 Hz, 2 H_{arom}), 6.91 (s, 1 H, pyrazole-H4), 4.12 (dd, J = 5.2, 5.0 Hz, 1 H, CHOH), 3.94 (s, 3 H, CO_2CH_3), 2.84 (d, J = 5.2 Hz, 2 H, CH_2), 2.02 (br s, 1 H, OH), 1.26 [d, J = 5.0 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 162.6 (s, CO_2CH_3), 144.8 (s, pyrazole-C3), 142.9 (s, C_q of Ar attached to C-pyrazole-N1), 142.5 (s, pyrazole-C5), 133.2 (d, CH_{arom}), 126.6 (d, CH_{arom}), 117.8 (s, $\text{C}\equiv\text{N}$), 112.6 (s, C_q , ArCN), 109.7 (d, pyrazole-C4), 67.1 (d, CHOH), 52.2 (q, CO_2CH_3), 35.4 (t, CH_2), 23.4 [q, $\text{CH}(\text{OH})\text{CH}_3$].

MS (EI): m/z = 285 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_3$: 286.1192; found: 286.1183.

Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.27; N, 14.78.

1-(2-Fluorophenyl)-3-methoxycarbonyl-5-(2-hydroxypropyl)pyrazole (3bg)

Yield: 439 mg (79%); pale yellow solid; mp 136–139 °C.

IR (Nujol): 3450, 1735, 1495 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.47–7.18 (m, 4 H_{arom}), 6.85 (s, 1 H, pyrazole-H4), 3.95 (m, 1 H, CHOH), 3.89 (s, 3 H, CO_2CH_3), 2.70–2.59 (m, 2 H, CH_2), 2.31 (br s, 1 H, OH), 1.11 [d, J = 5.2 Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 162.5 (s, CO_2CH_3), 156.6 (d, $^1J_{\text{C,F}}$ = 251 Hz, C_q , ArF), 144.0 (s, pyrazole-C3), 143.9 (s, pyrazole-C5), 131.1 (d, $^3J_{\text{C,F}}$ = 8 Hz, CH_{arom}), 129.2 (d, CH_{arom}), 126.4 (d, $^2J_{\text{C,F}}$ = 12 Hz, C_q of Ar attached to pyrazole N1), 124.5 (d, $^3J_{\text{C,F}}$ = 4 Hz, CH_{arom}), 116.3 (d, $^2J_{\text{C,F}}$ = 20 Hz, CH_{arom}), 108.0 (d, pyrazole-C4), 66.0 (d, CHOH), 51.7 (q, CO_2CH_3), 34.7 (t, CH_2), 22.6 [q, $\text{CH}(\text{OH})\text{CH}_3$].

^{19}F NMR (376 MHz, CDCl_3): δ = –110.78.

MS (EI): m/z = 278 [M^+].

HRMS (ESI+): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{FN}_2\text{O}_3$: 279.1145; found: 279.1167.

Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}_3$: C, 60.42; H, 5.43; N, 10.07. Found: C, 60.40; H, 5.38; N, 10.10.

1-Phenyl-3-methoxycarbonyl-5-(3-hydroxypropyl)pyrazole (11a)

Yield: 400 mg (77%); white solid; mp 83–85 °C.

IR (Nujol): 3440, 1745 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.46–7.40 (m, C_6H_5), 6.76 (s, 1 H, pyrazole-H4), 3.91 (s, 3 H, CO_2CH_3), 3.59 (t, J = 6.1 Hz, 2 H, CH_2OH), 2.72 (t, J = 8.2 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 2.16 (br s, 1 H, OH) 1.81 (dt, 2 H, J = 8.2, 6.1 Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.1 (s, CO_2CH_3), 145.2 (s, pyrazole-C3), 143.5 (s, C_q of Ph attached to pyrazole-N1), 139.1 (s, pyrazole-C5), 129.2 (d, CH_{arom}), 128.9 (d, CH_{arom}), 125.8 (d, CH_{arom}), 107.0 (d, pyrazole-C4), 61.3 (t, CH_2OH), 52.0 (q, CO_2CH_3), 31.2 (t, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 22.6 (t, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$).

MS (EI): m/z = 260 $[\text{M}^+]$.

HRMS (ESI+): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$: 261.1239; found: 261.1258.

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.63; H, 6.20; N, 10.80.

1-(4-Methylphenyl)-3-methoxycarbonyl-5-(3-hydroxypropyl)pyrazole (11b)

Yield: 438 mg (80%); white solid; mp 77–78 $^{\circ}\text{C}$.

IR (Nujol): 3445, 1740 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.30–7.24 (m, 4 H_{arom}), 6.75 (s, 1 H, pyrazole-H4), 3.92 (s, 3 H, CO_2CH_3), 3.60 (m, 2 H, CH_2OH), 2.70 (t, J = 8.0 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 2.40 (s, 3 H, ArCH_3), 2.13 (br s, 1 H, OH) 1.81 (t, J = 6.0 Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.1 (s, CO_2CH_3), 145.2 (s, pyrazole-C3), 143.3 (s, C_q of Ar attached to pyrazole-N1), 139.0 (s, pyrazole-C5), 136.6 (s, C_q , ArCH_3), 129.8 (d, CH_{arom}), 125.7 (d, CH_{arom}), 107.8 (d, pyrazole-C4), 61.4 (t, CH_2OH), 52.0 (q, CO_2CH_3), 31.3 (t, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 22.6 (t, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$).

MS (EI): m/z = 274 $[\text{M}^+]$.

HRMS (ESI+): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3$: 275.1396; found: 275.1411.

Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.71; H, 6.57; N, 10.26.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-(3-hydroxypropyl)pyrazole (11c)

Yield: 488 mg (77%); pale yellow solid; mp 95–97 $^{\circ}\text{C}$.

IR (Nujol): 3440, 1730 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.47–7.39 (m, 4 H_{arom}), 6.78 (s, 1 H, pyrazole-H4), 3.93 (s, 3 H, CO_2CH_3), 3.65–3.62 (m, 2 H, CH_2OH), 2.74 (t, J = 8.0 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 1.96 (br s, 1 H, OH) 1.88–1.81 (m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.9 (s, CO_2CH_3), 145.3 (s, pyrazole-C3), 143.8 (s, C_q of Ar attached to pyrazole-N1), 137.5 (s, pyrazole-C5), 134.8 (C_q , ArCl), 129.4 (d, CH_{arom}), 127.0 (d, CH_{arom}), 108.1 (d, pyrazole-C4), 61.3 (t, CH_2OH), 52.1 (q, CO_2CH_3), 31.1 (t, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 22.6 (t, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$).

MS (EI): m/z = 294 $[\text{M}^+]$.

HRMS (ESI+): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$: 295.0849; found: 295.0823.

Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_3$: C, 57.05; H, 5.13; N, 9.50. Found: C, 57.02; H, 5.10; N, 9.55.

Further elution gave the diynes **4** or **12** (see Supporting Information).

Octa-3,5-diyn-1,8-diol (4a)

Undistillable oil.

^1H NMR (400 MHz, CDCl_3): δ = 3.77 (t, J = 6.0 Hz, 4 H, $2 \times \text{CH}_2\text{OH}$), 2.56 (t, J = 6.0 Hz, 4 H, $2 \times \text{CH}_2$), 1.83 (br s, 2 H, $2 \times \text{OH}$).

^{13}C NMR (100 MHz, CDCl_3): δ = 74.7 (s, $\text{C}\equiv$), 66.8 (s, $\equiv\text{CCH}_2$), 60.8 (t, CH_2OH), 23.6 (t, CH_2).

MS (EI): m/z = 138 $[\text{M}^+]$.

Anal. Calcd for $\text{C}_8\text{H}_{10}\text{O}_2$: C, 69.54; H, 7.30. Found: C, 69.58; H, 7.33.

Deca-4,6-diyn-2,9-diol (4b)

Undistillable oil.

^1H NMR (400 MHz, CDCl_3): δ = 4.00–3.94 (m, 2 H, $2 \times \text{CHOH}$), 2.44 (d, J = 8.0 Hz, 4 H, $2 \times \text{CH}_2$), 2.39 (br s, 2 H, $2 \times \text{OH}$), 1.28 [d, J = 8.0 Hz, 6 H, $2 \times \text{CH}(\text{OH})\text{CH}_3$].

^{13}C NMR (100 MHz, CDCl_3): δ = 74.4 (s, $\text{C}\equiv$), 67.3 (s, $\equiv\text{CCH}_2$), 66.3 (d, CHOH), 29.7 (t, CH_2), 22.5 [q, $\text{CH}(\text{OH})\text{CH}_3$].

MS (EI): m/z = 166 $[\text{M}^+]$.

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$: C, 72.26; H, 8.49. Found: C, 72.30; H, 8.44.

Deca-4,6-diyn-1,10-diol (12)

Undistillable oil.

^1H NMR (400 MHz, CDCl_3): δ = 3.75 (t, J = 6.2 Hz, 4 H, $2 \times \text{CH}_2\text{OH}$), 2.40 (t, J = 8.1 Hz, 4 H, $2 \times \equiv\text{C}-\text{CH}_2$), 2.02 (br s, 2 H, $2 \times \text{OH}$), 1.79 (dt, J = 8.1, 6.2 Hz, 4 H, $\text{CH}_2\text{CH}_2\text{OH}$).

^{13}C NMR (100 MHz, CDCl_3): δ = 76.9 (s, $\text{C}\equiv$), 65.7 (s, $\equiv\text{CCH}_2$), 61.3 (t, CH_2OH), 31.0 (t, $\equiv\text{CCH}_2$), 15.7 (t, $2 \times \text{CH}_2\text{CH}_2\text{OH}$).

MS (EI): m/z = 166 $[\text{M}^+]$.

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$: C, 72.26; H, 8.49. Found: C, 72.21; H, 8.54.

Copper(I)-Catalysed Reaction between Tetrahydropyranyl Ether 7 and Hydrazonoyl Chloride 2a; 1-Phenyl-3-methoxycarbonyl-5-[2-(2-tetrahydropyrano)oxyethyl]pyrazole (8)

To a clear, colourless solution of tetrahydropyranyl ether **7**¹⁷ (0.31 g, 2.0 mmol) and Et_3N (0.20 g, 2.0 mmol) in anhyd CH_2Cl_2 (4 mL) was added CuCl (10 mg, 0.1 mmol) under vigorous magnetic stirring at 20 $^{\circ}\text{C}$. A solution of hydrazonoyl chloride **2a** (0.42 g, 2.0 mmol) in anhyd CH_2Cl_2 (4 mL) was added dropwise and the mixture was stirred at 20 $^{\circ}\text{C}$ for the time indicated in Table 2. The crude was filtered over a Celite pad, which was washed with CH_2Cl_2 (3×5 mL). The solvent was evaporated under reduced pressure to give **8**; yield: 500 mg (76%); thick, undistillable oil.

IR (Nujol): 3440 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.48–7.45 (m, 5 H, C_6H_5), 6.87 (s, 1 H, pyrazole-H4), 4.56 (m, 1 H, OCHO), 3.97–3.94 (m, 1 H, tetrahydropyranyl OCH_2), 3.93 (s, 3 H, CO_2CH_3), 3.73 (t, J = 8.0 Hz, 1 H, pyrazole CH_2O), 3.60 (dt, J = 8.0, 6.2 Hz, 1 H, tetrahydropyranyl OCH_2), 3.47 (m, 1 H, pyrazole CH_2O), 2.95 (t, J = 8.0 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{OTHP}$), 1.77–1.48 (m, 6 H, tetrahydropyranyl $\text{CH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR (100 MHz, CDCl_3): δ = 163.0 (s, CO_2CH_3), 143.7 (s, pyrazole-C3), 142.8 (s, C_q of Ph attached to pyrazole-N1), 139.1 (s, pyrazole-C5), 129.1 (d, CH_{arom}), 128.9 (d, CH_{arom}), 126.1 (d, CH_{arom}), 108.5 (d, pyrazole-C4), 98.9 (d, OCHO), 65.7 (t, tetrahydropyranyl OCH_2), 62.2 (t, pyrazole CH_2O), 52.0 (q, CO_2CH_3), 30.5 (t, $\text{CH}_2\text{CH}_2\text{OTHP}$), 26.9 (t, tetrahydropyranyl CH_2), 25.3 (t, tetrahydropyranyl CH_2), 19.4 (t, tetrahydropyranyl CH_2).

MS (EI): m/z = 330 $[\text{M}^+]$.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₁₈H₂₂N₂O₄: 331.1658; found: 331.1631.

Anal. Calcd for C₁₈H₂₂N₂O₄: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.49; H, 6.77; N, 8.40.

Acidic Cleavage of (Tetrahydropyrano)oxyethylpyrazole **8**; 1-Phenyl-3-methoxycarbonyl-5-(2-hydroxyethyl)pyrazole (**3aa**)

A solution of **8** (330 mg, 1 mmol) in AcOH/THF/H₂O (4:2:1, 3 mL) was stirred at 50 °C for 4 h. The solvent was evaporated in vacuo giving a light-brown oily residue that was taken up with CH₂Cl₂ (10 mL). The clear solution was washed with 5% aq NaHCO₃ (2 × 3 mL) and H₂O (2 × 3 mL). The organic layer was dried (Na₂SO₄) and filtered over a silica gel pad with CH₂Cl₂/MeOH (95:5) to afford the pyrazole **3aa**; yield: 216 mg (88%).

Glaser-Type Dimerisation of 3-Butyn-1-ol (**1a**); Octa-3,5-diyn-1,8-diol (**4a**)

A solution of 3-buten-1-ol (**1a**; 0.28 g, 4.0 mmol) and Et₃N (0.40 g, 4.0 mmol) in anhyd CH₂Cl₂ (8 mL) was treated with CuCl (20 mg, 0.2 mmol) under vigorous magnetic stirring and air bubbling at 20 °C. After 24 h, the TLC analysis of the bright yellow suspension did not show the presence of any product. Aq 30% H₂O₂ (5 µL, 49 µmol) was added, and the resulting dark-green mixture was filtered over a Celite pad, which was washed with CH₂Cl₂ (3 × 5 mL). Evaporation of the solvent under reduced pressure gave octa-3,5-diyn-1,8-diol (**4a**); yield: 248 mg (90%).

Glaser-Type Dimerisation of Tetrahydropyranyloether **7**; Octa-3,5-diyn-1,8-diol Bis-Tetrahydropyranyl Ether (**9**)

A solution of tetrahydropyranyl ether **7**¹⁷ (0.62 g, 4.0 mmol) and Et₃N (0.40 g, 4.0 mmol) in anhyd CH₂Cl₂ (8 mL) was treated with CuCl (20 mg, 0.2 mmol) under vigorous magnetic stirring for 5 h at 20 °C. The crude mixture was filtered over a Celite pad, which was washed with CH₂Cl₂ (3 × 5 mL), and the solvent was removed under reduced pressure to give **9**; yield: 529 mg (87%); mixture of unseparable racemic diastereoisomers; thick, undistillable oil.

¹H NMR (400 MHz, CDCl₃): δ = 4.65 (t, J = 4.0 Hz, 2 H, 2 × OCHO), 3.83 (td, J = 10.0, 7.0 Hz, 4 H, 2 × OCH₂CH₂), 3.55 (ddd, J = 10.0, 3.5, 2.5 Hz, 4 H, 2 × CH₂OTHP), 2.56 (t, J = 7.5 Hz, 2 H, ≡CCH₂), 2.50 (t, J = 7.5 Hz, 2 H, ≡CCH₂), 1.51–1.85 (m, 12 H, CH₂CH₂CH₂).

¹³C NMR (100 MHz, CDCl₃): δ = 98.9 (d, OCHO), 74.5 (s, C≡), 69.2 (s, ≡CCH₂), 65.2 (t, CH₂OTHP), 62.2 (t, OCH₂CH₂), 30.5 (t, ≡CCH₂), 25.4 (t, THPCH₂), 20.7 (t, THPCH₂), 19.3 (t, THPCH₂).

MS (EI): m/z = 306 [M⁺, 73%].

Anal. Calcd for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C, 70.61; H, 8.50.

Funding Information

The authors were financially supported by the Department of Chemistry of the Università degli Studi di Milano (PSR2020_DIP_005_PI).

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0042-1751770>.

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