Reactions of o-Quinone Methides with Halogenated 1H-Azoles: Access to Benzo[e]azolo[1,3]oxazines

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Abstract A simple route to the series of azolo-condensed benzo[e][1,3]oxazines such as 9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]oxazines, 9H-benzo[e]pyrazolo[5,1-b][1,3]oxazines, and 9H-benzo[e]imidazo[2,1-b][1,3]oxazines has been developed. The reaction proceeds through formation of an ortho-quinone methide intermediate followed by aza-Michael addition of the halogenoazoles to the o-quinone methide and intramolecular nucleophilic substitution.

Key words quinone methide, 1H-azoles, cascade reactions, aza-Michael reaction, benzo[e]azolo[1,3]oxazines

Condensed systems based on 1H-azoles attached with another heterocycle at the C–N bond are attracting the high attention of researchers. The principal reason for this interest is the high biological activity of some heteroannulated 1H-azoles such as [1,5]-fused 1,2,4-triazoles and pyrazoles, as well as [1,2]-fused imidazoles (Figure 1). Among the biologically relevant 1,2,4-triazoles, there are cytokine TNF-α and IL-6 inhibitors,1 the ligands of benzodiazepine receptors,2 modulators of γ-secretase,3 compounds effective against hepatitis B virus,4 and compounds exhibiting anti-convulsant5 and antihypertensive activities.6 One of the most attractive classes of antituberculosis compounds is [1,2]-annulated imidazoles, such as (6S)-2-nitro-6-[[4-(trifluoromethoxy)benzyl]oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (Pretomanid, PA-824) and its analogues.7 Furthermore, imidazo[2,1-b][1,3,4]thiadiazoles exhibit anticancer8 and antihyperlipidemic activity.9 Some of the heteroannulated pyrazoles possess antitubercular,10 anti-inflammatory11 and other types of activities.12

On the other hand, there is an ongoing need to establish new synthetic methodologies for the construction of different heterocycles, which are important for the development of the theoretical chemistry of heterocycles and for drug discovery.13 The most preferable tools towards the achievement of this goal seem to be cascade (or domino) reactions due to the benefits of their use.14

The cascade aza-Michael intramolecular nucleophilic substitution or addition reactions seem to be a useful sequence to produce nitrogen-containing heterocycles with...
high step economy. o-Quinone methides (o-QMs) can be efficiently used in these reactions as Michael acceptors. At the same time, in spite of numerous reports onaza-Michael reactions of o-QMs in biological systems, they are seldom used for the construction of heterocycles.

As part of our current studies on the development of new routes to heterocyclic systems from o-QMs, we focused our attention on the reaction of o-QMs with halogen-1H-azoles. In the case of presence of good leaving group such as halogen, near nucleophilic nitrogen atom azoles may be considered as 1,2-ambiphiles. Reactions of this type of azoles with o-QMs as 1,4-ambiphiles lead to different benz[e]azolo[1,3]oxazines (Scheme 1).

It was found that condensation of 3,5-dibromo-1,2,4-triazole (1) with a series of o-QM precursors 2 by heating equimolar quantities of the starting materials in DMF in the presence of K$_2$CO$_3$ gave benz[e][1,2,4]triazolo[5,1-b][1,3]oxazines 3 in good yields (Table 1). o-QMs were generated from o-hydroxybenzyl alcohols 2a-c, Mannich base 2d, and quaternary ammonium salts 2e-1n derived from phenols. The reactions were performed in DMF under reflux for completely thermal decomposition of the o-QM precursors. Products can be easily purified from impurities by single recrystallization, chromatographic purification is not usually required. The reaction was performed with comparable yields on several different scales (up to 20 mmol). It should be noted that none of the products of the o-QM oligomerization, which are obtained in the usual pyrolytic methods were detected. In the case of esters 2i and 2n low yields of the products 3i (24%) and 3n (39%) were caused by partial hydrolysis of the ester group (Table 1, entries 9,14). The sterically hindered triazolobenzoxazines 3a,k,l were obtained in good yields, indicating that steric hindrance had no obvious influence on the efficiency of this method (entries 1,11,12). We could not obtain product 3m from the methiodide of 2-[dimethylamino]methyl]-4-nitrophenol. Nevertheless, in the reaction with more reactive precursor of o-QM 2m, the corresponding triazolobenzoxazine 3m was obtained in 64% yield (entry 13). In order to broaden the scope of the present method, this protocol was attempted using bis-Mannich base 2o derived from hydroquinone. As a result, novel heterocyclic system 3o was prepared in 72% yield (entry 15). Besides, 3-chloro-1,2,4-triazole can be also involved in this reaction instead of 3,5-dibromo-1,2,4-triazole (1) (entry 16).

In the absence of a base, the reaction can be stopped at the stage of 2-(1H-1,2,4-triazol-1-ylmethyl)phenols 4a,b (Scheme 2). It is interesting to note that the generation of o-QM from Mannich base 2p took place at milder conditions (in ethanol under reflux), which can be explained by increased conjugation in this intermediate.

The mechanism of the reaction is believed to involve the formation of the o-QM intermediate A, which is generated in situ from the corresponding precursor 2. Subsequentaza-Michael addition of the o-QM with 1 and intramolecular nucleophilic substitution via formation of the Meisenheimer-type complex B affords the expected benz[e][1,2,4]triazolo[5,1-b][1,3]oxazines 3 (Scheme 3). The driving force of the reaction is the resulting rearomatization of the benzene ring and the entropy factor, favoring intramolecular versus intermolecular nucleophilic addition-elimination reactions in the 1,2,4-triazole moiety. During the reaction only a small concentration of o-QM is produced, which prevents its oligomerization and leads to good yields of the products of N-hydroxybenzylolation. K$_2$CO$_3$ is required to facilitate the o-QM generation and subsequent cyclization to the benz[e][1,2,4]triazolo[5,1-b][1,3]oxazine ring system. It should be noted that the alkylation of 3,5-dibromo-1,2,4-triazole (1) with o-QM precursors may give rise to two isomeric triazolobenzoxazines 3 and 5. However, in all cases, the alkylation occurs at N1(2) rather than N4, reflecting the higher nucleophilicity of N–N systems (α-effect).

The generation of the o-QM under reaction conditions from Mannich base 2d was indirectly confirmed by its trapping with N-vinyl-2-pyrrolidone with formation of the corresponding Diels–Alder cycloadduct 6 in 72% yield (Scheme 4). However, a stepwise reaction route without formation of
α-QM intermediate via nucleophilic substitution of leaving group by triazole moiety and ring closure could not be completely rejected.

The reaction of 1 and 4-chloro-2,6-bis(hydroxymethyl)phenol (2q) due to the tandem generation of the α-QM gives benzoxazine 3q containing two 1,2,4-triazole moieties (Scheme 5). The reaction is a domino-process that in-

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-QM precursor</th>
<th>Product</th>
<th>Entry</th>
<th>α-QM precursor</th>
<th>Product</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>9</td>
<td>MeOOC-NMe3 I</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>10</td>
<td>MeOOC-NMe3 I</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
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<td>11</td>
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<td>13</td>
<td>2-Ad</td>
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<td>8</td>
<td></td>
<td></td>
<td>16</td>
<td>2-Ad</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (2.9 mmol), α-QM precursor 2 (2.9 mmol), and K2CO3 (8.7 mmol) were refluxed in DMF (10 mL) for 4 h.

*Reaction was carried out in mixture of MeCN and H2O (2:1) at 80 °C without K2CO3.

*Two equivalents of 3,5-dibromo-1,2,4-triazole (1) were used.

*3-Chloro-1,2,4-triazole was used instead of 3,5-dibromo-1,2,4-triazole (1).
It was difficult to stop the reaction at the stage of the for-

type additions, and one nucleophilic substitution reaction.

includes five steps: two dehydration reactions, two Michael-
type additions, and one nucleophilic substitution reaction. It was difficult to stop the reaction at the stage of the for-
mation of the corresponding 1,2,4-triazol-1-ylmethylphe-
nol even in the absence of a base. The formation of the product 3q indicates a greater rate of 1,4-addition rather than intramolecular nucleophilic substitution.

Magnetic nonequivalence of the 1,2,4-triazole carbon atoms in the compounds 4a,b and also 3q (8 signals for 4a and 10 signals both for 4b and 3q in the aromatic region of $^{13}$C NMR spectra) indicates that the alkylation occurred at the N(2) atom of the 1,2,4-triazole ring rather than N(4). The same regioselectivity was observed in reactions of 1 with p-
hydroxybenzyl alcohols 7 as precursors of p-quinoime methides C, which allow to prepare the 4-[(1,2,4-triazol-1-

yl)methyl]phenols 8a–c in good yields (Scheme 6).

We have also applied the developed method to the syn-
thesis of 9H-benzo[e]pyrazolo[5,1-b][1,3]oxazines 10a–d from salicylic alcohols 2r–u and 3,4,5-tribromopyrazole (9a) and 3,5-dibromo-4-nitropyrazole (9b) (Table 2). In the case of 9b, the presence of a base is not required because the nitro group in the pyrazole moiety significantly increases the reactivity of nucleophilic substitution and the ability of the bromine atoms to be eliminated.

The reaction of ammoniumphenolate 2m and 2-

bromo-1H-imidazole-4,5-dicarbonitrile (11a) or dimethyl 2-

bromo-1H-imidazole-4,5-dicarboxylate (11b) in aqueous acetonitrile leads to 5H-benzo[e]imidazol[2,1-b][1,3]ox-

azines 12a,b in 47% and 57% yield, respectively (Scheme 7). At the same time, reactions of salicylic alcohols with 2-bro-

mo-, 2-chloro-, 2-(methylthio)-1H-benzo[d]imidazoles or 2-

bromo-4,5-diphenyl-1H-imidazole require harsh condi-
tions both for efficient generation of o-QM intermediates and for successful further cyclization. It should be noted that the reaction of the imidazoles 11a,b with other precur-

sors of the o-QMs (salicylic alcohols, phenolic Mannich bas-
es, quaternary salts) in refluxing aqueous acetonitrile did not proceed, and in boiling DMF a complex mixture of un-

identified products was obtained.

The IR spectra of compounds 3a–q, 10b–d, and 12a,b show the absence of stretching vibration bands for an O–H bond, which supports the cyclic structure of the com-

pounds obtained. The methylene signals in $^1$H NMR spectra shift downfield due to the electron-withdrawing azole group and appear as singlets in the region of 5.21–5.64
In conclusion, a useful method for the synthesis of 9H-benzo[e]1,2,4-triazolo[5,1-b][1,3]oxazines, 9H-benzo[e]pyrazolo[5,1-b][1,3]oxazines, and 5H-benzo[e]imidazo[2,1-b][1,3]oxazines based on cascade aza-Michael and intramolecular nucleophilic substitution reactions was developed. Their synthesis by the suggested procedure does not require an excess of any reagents, includes the use of available reagents, simple workup procedure, scalability, and good functional group tolerance. The Michael-type addition reaction of o-QMs and azoles is advantageous due to its higher regioselectivity compared to alkylation reactions using alkyl halides or alkyl sulfates. Besides, due to the presence of the bromine atoms some of the prepared products may be valuable intermediates for obtaining aryl-substituted azolobenzoxazines by C–C cross-coupling methods.

Melting points were determined by capillary method on a SRS OptiMelt MPA100 apparatus and are uncorrected. FTIR-spectra were taken on a Shimadzu FTIR-8400S spectrophotometer as KBr pellets. 1H and 13C NMR spectra (including DEPT-135 experiments) were recorded on a Jeol JNM-ECX 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d6 or CDCl3 solutions, relative to residual solvent signals (CDCl3 δ = 7.26 ppm [1H], CDCl3 δ = 77.0 ppm [13C]; DMSO-d6 δ = 2.50 ppm [1H], δ = 39.5 ppm [13C]). Chemical shifts and coupling constants were recorded in units of parts per million and hertz, respectively. Mass spectra were recorded on a Finnigan Trace DSQ chromatofourier mass spectrometer with direct introduction of the sample into the ion source (EI, 70 eV, mass-selective detector). Elemental analyses were carried out on a Euro Vector EA-3000 automatic CHN analyzer.

In the 13C NMR spectra, the signals of the methylene carbon atoms appear at 44.6–47.0 ppm. The IR spectra of compounds 4a–b show a broad absorption band in the range 3400–3200 cm⁻¹ corresponding to the stretching vibration of a hydroxyl group associated with hydrogen bonding and singlets at δ = 9.10 and 9.21 in the 1H NMR spectra were assigned to OH protons. In the case of compounds 8a–c, absorption of the phenolic hydroxyl groups was observed as strongly broadened diffuse bands with several maxima in the region of 3000–3500 cm⁻¹. The number of protons that were directly linked to 13C atoms, inferred from DEPT spectra, was in accordance with the presented structures.

Table 2 Scope of the Benzo[e]pyrazolo[5,1-b][1,3]oxazine Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>o-QM precursor</th>
<th>Product</th>
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<tbody>
<tr>
<td>1a</td>
<td>MeO</td>
<td>10a, 65%</td>
</tr>
<tr>
<td>2c</td>
<td>MeO</td>
<td>10c, 53%</td>
</tr>
<tr>
<td>3e</td>
<td>MeO</td>
<td>10e, 80%</td>
</tr>
<tr>
<td>4f</td>
<td>MeO</td>
<td>10f, 75%</td>
</tr>
</tbody>
</table>

*Reaction conditions: 9a (2.5 mmol), o-QM precursor 2r or 2s (2.5 mmol), and K2CO3 (7.5 mmol) were refluxed in DMF (10 mL) for 5 h.

Scheme 7 Synthesis of benzo[e]imidazo[2,1-b][1,3]oxazines 12. Reagents and conditions: 11a or 11b (1.2 mmol) and o-QM precursor 2m (1.2 mmol) were refluxed in H2O (1.5 mL) and MeCN (3 mL) for 4 h.

2′-Bromospiro[adamantane-2,9′-benzo[e]1,2,4]triazolo[5,1-b][1,3]oxazine (3a)

Yield: 658 mg (61%); colorless crystals; mp 214–216 °C (DMF).

1H NMR (400 MHz, DMSO-d6): δ = 7.90 (d, J = 7.8 Hz, 1 H, Ar), 7.42–7.49 (m, 2 H, Ar), 7.32–7.36 (m, 1 H, Ar), 2.49–2.54 (m, 4 H, Ad), 2.01–2.05 (m, 2 H, Ad), 1.80–1.87 (m, 4 H, Ad), 1.64–1.69 (m, 4 H, Ad).

13C NMR (100 MHz, DMSO-d6): δ = 157.0 (C), 152.2 (C), 135.5 (C), 130.0 (CH), 129.6 (C), 127.9 (C), 126.0 (CH), 118.5 (CH), 69.2 (C-2, Ad), 37.9 (CH2, Ad), 35.1 (2 × CH, Ad), 35.0 (2 × CH2, Ad), 33.4 (2 × CH2, Ad), 26.7 (CH, Ad), 26.5 (CH, Ad).
2-Bromo-5-phenyl-9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]oxazine (3b)

Yield: 683 mg (67%); colorless crystals; mp 219–221 °C (EtOH).

IR (KBr): 3048, 2955, 1717, 1597, 1558, 1524, 1497, 1462, 1431, 1404, 1288, 1258, 1200, 1151, 987, 895, 845, 764, 721, 694 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): 7.35–7.40 (m, 4 H, Ar), 7.30 (d, J = 8.2 Hz, 1 H, H-5), 7.20 (d, J = 8.2 Hz, 1 H, H-6), 5.28 (s, 2 H, CH2), 1.26 (s, 9 H, t-C6H13).

Anal. Calcd for C17H22BrN3O: C, 56.05; H, 6.09; N, 13.64. Found: C, 56.16; H, 3.53; N, 12.28. C, 56.22; H, 3.48; N, 13.58.

2-Bromo-7-tert-butyl-9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]oxazine (3f)

Yield: 685 mg (69%); colorless crystals; mp 185–186 °C (EtOH).

IR (KBr): 3024, 2965, 2905, 1601, 1562, 1520, 1497, 1462, 1431, 1404, 1288, 1258, 1200, 1151, 987, 895, 845, 764, 721, 694 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): δ = 7.13–7.28 (m, 8 H, Ar), 5.24 (s, 2 H, CH2N), 3.91 (s, 2 H, CH2Ph).

13C NMR (100 MHz, DMSO-δ6): δ = 154.9 (C), 148.5 (C), 145.7 (C), 137.1 (C), 126.9 (CH), 124.8 (CH), 116.9 (CH), 115.4 (C), 46.4 (CH3N), 34.8 [C(CH3)3], 31.6 [CH3(CH2)4].

Anal. Calcd for C51H62BrN6O: C, 56.07; H, 4.98; N, 10.77. Found: C, 55.96; H, 5.26; N, 10.82.

Methyl 2-Bromo-9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]oxazine-7-carboxylate (3i)

Yield: 216 mg (24%); colorless crystals; mp 251–253 °C (EtOAc).

IR (KBr): 3034, 2955, 1717, 1597, 1558, 1524, 1497, 1439, 1300, 1277, 1250, 1195, 1177, 1126, 991, 914, 768 cm⁻¹.
2-Bromo-7-methoxy-9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]oxazine (3j)

Yield: 975 mg (84%); colorless crystals; mp 241–242 °C (EtOH–DMSO).

IR (KBr): 3200, 2286–2296 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 8.03 (d, J = 1.8 Hz, H, H-8), 7.93 (dd, J = 8.7, 1.8 Hz, 1 H, H-6), 7.42 (d, J = 8.7 Hz, 1 H, H-5), 5.35 (s, 2 H, CH2), 3.84 (s, 3 H, CH3).

13C NMR (100 MHz, DMSO-d6): δ = 153.6 (C), 154.0 (C), 141.6 (C), 137.1 (C), 118.4 (CH), 116.9 (C), 115.8 (CH), 112.2 (CH), 56.2 (CH3).


Ethyl 8-Bromo-2-methyl-3,11-dihydro[1,2,4]triazolo[5,1-b][1,3]oxadiazole-5,6-epox Idle (3n)

Yield: 427 mg (39%); white crystals; mp 269–270 °C (DMSO).

IR (KBr): 3300–3100, 2978, 2932, 1701, 1500, 1477, 1425, 1385, 1288, 1215, 1200, 1150, 1057, 1030, 991, 802, 783 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 12.09 (br s, 1 H, NH), 7.36 (d, J = 8.7 Hz, 1 H, Ar), 7.04 (d, J = 8.7 Hz, 1 H, Ar), 5.64 (s, 2 H, CH2), 4.24 (q, J = 7.1 Hz, 2 H, CH2), 2.57 (s, 3 H, CH3), 1.32 (t, J = 7.1 Hz, 4 H, CH2CH3).

13C NMR (100 MHz, DMSO-d6): δ = 153.3 (C), 152.2 (C), 144.6 (C), 137.3 (C), 125.4 (C), 118.8 (CH), 118.3 (C), 46.4 (CH3).


2.9-Dibromo-6,13-dihydrobis[1,2,4]triazolo[5,1-b:5,1-b']benzo[b]-1,4,5,6-tetrahydro-2,3-benzopyran-4-one (3o)

The title compound was synthesized by the general procedure using 2 equiv of 1; yield: 890 mg (72%); colorless crystals; mp > 350 °C (DMF, dec.).

IR (KBr): 3063, 2935, 1562, 1528, 1501, 1440, 1304, 1237, 1300, 1281, 1242, 1196, 1161, 1134, 987, 914, 887, 729, 717 cm–1.

1H NMR (400 MHz, DMSO-d6, at 140 °C): δ = 7.39 (s, 2 H, Ar), 5.35 (s, 4 H, 2 × CH2).

13C NMR (100 MHz, DMSO-d6, at 145 °C): δ = 154.1 (2 C), 154.1 (2 C) 137.4 (2 C), 117.9 (2 × CH), 116.4 (2 C), 46.3 (2 × CH3).


2-Bromo-7-nitro-9H-benzo[e][1,2,4]triazolo[5,1-b][1,3]oxazine (3m)

Yield: 551 mg (64%); light-yellow crystals; mp 236–238 °C (EtOH–MeCN, 1:2).

IR (KBr): 1597, 1557, 1518, 1479, 1404, 1346, 1287, 1217, 1184, 1150, 1084, 930, 893, 839, 820, 748, 716, 656 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 8.04 (d, J = 2.8 Hz, 1 H, H-8), 8.23 (dd, J = 2.8, 9.2 Hz, 1 H, H-6), 7.54 (d, J = 9.2 Hz, 1 H, H-5), 5.38 (s, 2 H, CH2).

13C NMR (100 MHz, DMSO-d6): δ = 153.5 (C), 149.5 (C), 145.4 (C), 137.8 (C), 134.3 (C), 127.8 (CH), 126.2 (CH), 116.3 (C), 46.0 (CH3), 40.8 (3 × CH2), 37.1 (C, Ad), 36.8 (3 × CH2), 28.8 (3 × CH), 21.0 (CH3).

MS (EI): m/z (%): 321 (100, [M]+), 320 (22, [M – H]+), 278 (8), 264 (62), 236 (17), 228 (15), 221 (7), 200 (11), 165 (16).

**Synthesis**  
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2-Bromo-7-chloro-5-[(3,5-dibromo-1H-1,2,4-triazol-1-yl)methyl]-9H-benzo[e][1,2,4]triazolo[5,1-b][1,1]loxazine (3q)

3,5-Dibromo-1,2,4-triazole (1; 1.134 g, 5.00 mmol) and 4-chloro-2,6-bis(hydroxymethyl)phenol (2q; 472 mg, 2.5 mmol) were refluxed for 5 h in DMF (10 mL). After completion of the reaction, the mixture was cooled and poured into H2O (30 mL). The precipitate formed was collected by filtration, washed with H2O, dried, and recrystallized: yield: 722 mg (55%); colorless crystals; mp 258–260 °C (DMF).

IR (KBr): 2924, 1601, 1470, 1431, 1292, 1261, 1180, 1150, 1065, 987, 864 cm–1.


1H NMR (400 MHz, DMSO-d6): δ = 11.46 (s, 1 H, NH), 9.21 (s, 1 H, OH), 7.52 (s, 1 H, NHCO), 7.22 (d, J = 8.7 Hz, 1 H, Ar), 6.78 (d, J = 8.7 Hz, 1 H, Ar), 5.48 (s, 2 H, CH2N), 3.45 (td, J = 6.9, 2.3 Hz, 2 H, CH2), 3.01 (t, J = 6.9 Hz, 2 H, CH2).

13C NMR (100 MHz, DMSO-d6): δ = 162.3 (C=O), 150.4 (C), 139.4 (C), 132.5 (C), 131.3 (C), 128.8 (C), 125.7 (C), 117.1 (C), 115.0 (CH), 114.5 (CH), 110.3 (C), 46.0 (CH2), 41.5 (CH2), 22.8 (CH2).


1-(6,8-Di-tert-butylchroman-2-yl)pyrrolidin-2-one (6)

Mannich base 2d (1 g, 3.8 mmol) and N-vinyl-2-pyrrolidinone (0.5 mL, 0.48 g, 4.3 mmol) in DMF (10 mL) were refluxed for 12 h. After completion of the reaction, the solution was cooled and poured into H2O (30 mL). The precipitate formed was collected by filtration, washed with H2O, dried, and recrystallized from MeOH; yield: 0.9 g (72%); colorless crystals; mp 134–135 °C.

IR (KBr): 2955, 2924, 2872 (C–H ν-ν), 1701 (C=O), 1476, 1458, 1449, 1423, 1362, 1281, 1288, 1221, 1200, 1167, 1125, 1098, 1045, 1003 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.16 (d, J = 2.3 Hz, 1 H, Ar), 6.93 (d, J = 2.3 Hz, 1 H, Ar), 5.87 (dd, J = 11.0, 2.3 Hz, 1 H, CHNO), 3.58–3.64 (m, 1 H, J = 3.4–3.52 (m, 1 H), 3.07 (dd, J = 15.6, 12.4, 6.4 Hz, 1 H, CH2), 2.85 (dd, J = 16.5, 5.5, 2.3 Hz, 1 H), 2.49 (t, J = 8.2 Hz, 2 H), 2.05–2.17 (m, 3 H), 1.96–2.01 (m, 1 H), 1.36 (s, 9 H, t-C9H18), 1.29 (s, 9 H, t-C9H18).

13C NMR (100 MHz, CDCl3): δ = 155.8 (C=O), 150.8 (C–O), 142.5 (C), 137.0 (C), 129.1 (CH2), 121.2 (CH2), 120.2 (C), 78.0 (CHNO), 42.7 (CH2), 35.1 (C), 34.3 (C), 31.7 [C(CH3)]3, 30.9 [C(CH3)]3, 25.9 (CH2), 25.5 (CH2), 18.5 (CH3).


4-[(3,5-Dibromo-1H-1,2,4-triazol-1-yl)methyl]phenol8; General Procedure

3,5-Dibromo-1,2,4-triazole (1; 658 mg, 2.9 mmol) and p-quionone methide precursor 7 (2.9 mmol) were refluxed for 4 h in DMF (10 mL). Products were isolated analogously to compound 4a.

4-[(3,5-Dibromo-1H-1,2,4-triazol-1-yl)methyl]phenol8 (8a)

Yield: 864 mg (79%); colorless crystals; mp 125–127 °C (EtOH).

IR (KBr): 3500–3000 (OH), 2980, 1603, 1530, 1454, 1435, 1349, 1352, 1271, 1213, 1161, 1069, 1036 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 9.04 (s, 1 H, OH), 6.85 (d, J = 1.6 Hz, 1 H, H-3), 6.73 (d, J = 8.0 Hz, 1 H, H-5), 6.63 (dd, J = 8.0, 1.6 Hz, 1 H, H-6), 5.22 (s, 2 H, CH2N), 3.95 (q, J = 7.2 Hz, 2 H, CH2CH3), 1.28 (t, J = 7.2 Hz, 3 H, CH3CH3).

13C NMR (100 MHz, DMSO-d6): δ = 171.3 (C), 147.2 (C), 139.8 (C), 131.0 (C), 125.7 (C), 121.2 (CH2), 116.2 (CH), 114.1 (CH), 64.2 (CH2), 53.5 (CH3), 15.2 (CH3).


4-[(3,5-Dibromo-1H-1,2,4-triazol-1-yl)methyl]-2,6-dimethoxyphenol (8b)

Yield: 707 mg (62%); colorless crystals; mp 154–156 °C (EtOH).

IR (KBr): 3500–3100 (OH), 3011, 2967, 2940, 2841, 1616, 1591, 1520, 1458, 1431, 1375, 1356, 1239, 1263, 1244, 1223, 1190, 1159, 1117, 1076, 1042, 827, 770 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): δ = 8.51 (br s, 1 H, OH), 6.55 (s, 2 H, H-3, 5), 5.23 (s, 2 H, CH2), 3.70 (s, 6 H, 2 × CH3O).

13C NMR (100 MHz, DMSO-δ6): δ = 155.9 (C), 139.8 (C), 130.8 (C), 128.5 (2 × CH), 125.3 (2 C), 125.1 (C), 53.3 (CH3), 17.1 (2 × CH3).

MS for 8Br EI: m/z (%) = 378 (22, [M⁺]), 309 (5, [M – Br⁺]), 240 (20), 149 (37), 121 (94), 107 (27), 91 (38, [C6H4Br⁺]), 77 (100).


4-[(3,5-Dibromo-1H-1,2,4-triazol-1-yl)methyl]-2,6-dimethylphenol (8c)

Yield: 838 mg (80%); colorless crystals; mp 185–186 °C (EtOH).

IR (KBr): 3500–3200 (OH), 16.3, 1489, 1452, 1383, 1354, 1337, 1312, 1273, 1211, 1155, 1069, 962, 768 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): δ = 8.36 (s, 1 H, OH), 6.82 (s, 2 H, H-3, 5), 5.16 (s, 2 H, CH2), 2.11 (s, 6 H, 2 × CH3O).

13C NMR (100 MHz, DMSO-δ6): δ = 153.9 (C), 139.8 (C), 130.8 (C), 128.5 (2 × CH), 125.3 (2 C), 125.1 (C), 53.3 (CH3), 17.1 (2 × CH3).

MS for 9Br EI: m/z (%) = 391 (14, [M⁺]), 167 (100, [M – C6Br6N4⁺]).

Anal. Calcd for C9H6BrN6O3: C, 33.62; H, 2.82; N, 10.69. Found: C, 33.71; H, 2.76; N, 10.75.

9H-Benz[e]pyrazolo[5,1-b][1,3]oxazin-10; General Procedure

3,4,5-Tribromopyrazole (9a): 762 mg, 2.5 mmol) or 3,5-dibromo-4-nitrotiazole (9b: 677 mg, 2.5 mmol), o-quinone methide precursor 2 (2.5 mmol) and K2CO3 (only for 9a, 1.035 g, 7.5 mmol) were refluxed for 4 h in DMF (10 mL). Product was isolated analogously to compound 4a.

(2,3-Dimethoxy-7-bromo-9H-benz[e]pyrazolo[5,1-b][1,3]oxazin-5-yl)methanol (10a)

Yield: 634 mg (65%); colorless crystals; mp 229–230 °C (MeOH–DMF; 3:1).

IR (KBr): 3500–3300, 2931, 2870, 2839, 1624, 1609, 1570, 1531, 1481, 1435, 1389, 1358, 1234, 1188, 1142, 1084, 1045, 1022, 891, 856, 737 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): δ = 6.98 (s, 1 H, Ar), 6.79 (s, 1 H, Ar), 5.36 (br s, 1 H, OH), 5.21 (s, 2 H, CH2), 4.58 (s, 2 H, CH2OH), 3.72 (s, 3 H, CH3O).

13C NMR (100 MHz, DMSO-δ6): δ = 156.2, 145.7, 138.1, 132.1, 127.1, 116.5, 113.6, 110.0, 76.0 (C-3), 57.4, 56.0, 46.7 (CH2N).

MS for 10Br EI: m/z (%) = 373 (32, [M⁺]), 343 (4, [M – NO⁺]), 294 (2, [M – Br⁺]), 210 (50), 184 (25), 156 (18, [C6H4Br⁺]), 131 (32), 113 (58), 89 (38), 77 (100, [C6H4⁺]).


2,7-Dibromo-3-nitro-9H-benz[e]pyrazolo[5,1-b][1,3]oxazine (10d)

Yield: 703 mg (75%); light-yellow crystals; mp 244–260 °C (DMF).

IR (KBr): 3055, 1593, 1562, 1528, 1491, 1477, 1420, 1400, 1350, 1250, 1173, 1115, 1065, 918, 833 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): δ = 7.67 (d, J = 2.3 Hz, 1 H, H-8), 7.58 (dd, J = 8.7, 2.3 Hz, 1 H, H-6), 7.34 (d, J = 8.7 Hz, 1 H, H-5), 5.27 (s, 2 H, CH2).

13C NMR (100 MHz, DMSO-δ6): δ = 146.0 (C), 145.1 (C), 132.8 (CH), 130.9 (CH), 123.1 (C), 119.5 (CH), 118.6 (C), 118.0 (C), 116.5 (C-3), 46.1 (CH3N).

MS for 10Br EI: m/z (%) = 434 (37, [M⁺]), 373 (32, [M – Br⁺]), 294 (2, [M – Br⁺]), 210 (50), 184 (25), 156 (18, [C6H4Br⁺]), 131 (32), 113 (58), 89 (38), 77 (100, [C6H4⁺]).


7-Nitro-5H-benz[e]imidazo[2,1-b][1,3]oxazines 12; General Procedure

Imidazole 11a or 11b (1.2 mmol) and o-quinone methide precursor 2m (303 mg, 2.5 mmol) were refluxed for 4 h in a mixture of H2O (1.5 mL) and MeCN (3 mL). Product was isolated analogously to compound 4a.

7-Nitro-5H-benz[e]imidazo[2,1-b][1,3]oxazine-2,3-dicarboximide (12a)

Yield: 151 mg (47%); yellow crystals; mp 258–260 °C (MeCN–H2O, 2:1, dec.).

IR (KBr): 3074, 3047, 2928, 2233 (C=O), 1597, 1547, 1525 (NO2), 1504, 1481, 1350 (NO2), 1319, 1304, 1273, 1223, 1188, 1130, 1092, 930, 868, 852, 748, 706 cm⁻¹.

1H NMR (400 MHz, DMSO-δ6): δ = 8.46 (d, J = 2.7 Hz, 1 H, H-6), 8.25 (dd, J = 9.2, 2.7 Hz, 1 H, H-8), 7.57 (d, J = 9.2 Hz, 1 H, H-9), 5.48 (s, 2 H, CH2).

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13C NMR (100 MHz, DMSO-d6): δ = 151.8 (C), 147.8 (C), 144.9 (C), 125.7 (CH), 124.2 (CH), 118.7 (CH), 118.3 (C), 116.5 (C), 116.5 (C), 108.8 (CN), 108.6 (CN), 44.6 (CH).


Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588411.

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