Efficient One-Pot Synthesis of Triazole-Linked Morpholinone Scaffolds by CuAAC in the Presence of 18-Crown-6

A. Mayooufi, M. Romdhani-Younes, J. Thibonnet

Key words: click chemistry, iodolactonization, morpholinones, azides, 1,2,3-triazole, one-pot procedure

The synthesis of five- and six-membered nitrogen-containing heterocycles, such as morpholinones and 1,2,3-triazoles, has received considerable attention, and these structures constitute important classes of biologically active compounds.

Various morpholinone-containing compounds have been reported in the past decade with a range of biological properties (Scheme 1). For example, compound A exhibits antifungal and antibacterial activities against four bacteria and seven fungal species. Morpholinone B was recently found to be an inhibitor of the MDM2–p53 protein–protein interaction. It is important to note that 1,2,3-triazole based heterocycles have become a cornerstone of medicinal chemistry because of their important biological activities. For example, compound C exhibits potent anticancer activity. Compound D was found to have good TNF-α inhibitory activity. Antiviral compound E exhibits cytostatic activity in the high micromolar range, and compound F shows potent antibacterial activity against both Gram-positive and Gram-negative bacteria. In addition, a series of thiazolidinediones with triazole substitution show antidiabetic and anticancer activity properties.

Given the promising biological properties and synthetic applications of these heterocycles, it appeared interesting to consider the combination of these moieties, with the aim to access novel more biologically effective compounds. A consequence, the development of effective and practical methods for the construction of morpholines with 1,2,3-triazoles units appeared to be a worthwhile goal.

In our previous work, we have synthesized numerous heterocycles by using coupling/cyclization tandem reactions. In a continuation of our research devoted to the development and diversification of new classes of heterocycles, we report herein the construction of iodomorpholinone 5 through electrophilic iodolactonization of acid 2. In addition, introduction of an iodo- functionality provides a useful route for the synthesis of novel morpholinones, incorporating the 1,2,3-triazole moiety, with good yields.

Initially, the starting acids 2 and 4 were prepared from allylamine in three steps (Scheme 2). Allylamine was tosylated under standard conditions, providing the corresponding tosyl-functionalized amine. This amine was then alkylated by following Raghunathan’s protocol using ethyl bromoacetate, affording ethyl N-allyl-N-tosylglycinate 1 in 80% yield over two steps. Saponification of ester 1 was achieved using 12% KOH, leading to the corresponding acid 3 in quantitative yield. The synthesis of compound 4 was achieved in two steps. First, the N-tosylated allyl amine was reacted with methyl acrylate in MeCN in the presence of a substoichiometric amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), resulting in an aza-Michael addition reaction, as developed by Kim’s group. Having synthesized the ester 3 in good yield (88%), the next task was to convert the ester into its corresponding acid. The saponification of ester 3 was achieved with LiOH in a MeOH/H2O mixture to afford the desired acid 4 in quantitative yield. Compounds 3 and 4 were characterized by comparison with the published NMR spectra (see the Supporting Information).
We next explored the reactivity of amino acid 2 in the iodolactonization reaction. Iodocyclization of alkynes or alkenes represents a useful method for the preparation of important heterocycles, and a number of methods have been reported for the construction of functionalized cyclic compounds through halolactonization such as azetidines and pyrrolidines, benzo[d]phenazines, lactones, oxazolidin-2-ones, and other heterocycles. The results of the iodolactonization reaction of 3-aminopropanoic acid when stored in the refrigerator. This work led us to investigate the iodocyclization of 3-amino propanoic acid 4. Thus, acid 4 was treated with I2 (1.5 equiv), Na2CO3 (2 equiv) and AgNO3 (1 equiv) in CHCl3 at 25 °C and, after 2 hours, complete iodolactonization was achieved, leading to the iodo-1,4-oxazepan-7-one 6 in 56% yield (Scheme 3). It should be noted that product 6 is unstable. This product must be immediately purified, and it degrades quickly even when stored in the refrigerator.

**Scheme 1** Selected biologically active triazole and morpholinone units and retrosynthetic strategy for the sequential synthesis of morpholinones incorporating the 1,2,3-triazole moiety

**Scheme 2** Preparation of acids 2 and 4

**Scheme 3** Iodocyclization of acid 4
We then focused on the installation of 1,2,3-triazole groups into the morpholinone scaffold through CuAAC-based multicomponent reactions (MCR). MCRs are important and effective in carbon–nitrogen bond formation because of their considerable economic and ecological interests. These reactions have become important tools for the organic chemist to generate complex molecules that find many applications in drug discovery. In this context, the reactivity of halomorpholinones has been widely studied with sodium azide and terminal alkynes by using this one-pot two-step sequence. Although we tested various conditions for the synthesis of 1,2,3-triazoles that are described in the literature, in our case no desired product was observed. On the basis of these results, we turned our attention to the preparation of novel morpholinones, incorporating the 1,2,3-triazoles moiety through the more classical two-step route, as shown in Scheme 4.

Thus, we examined nucleophilic substitution of the remaining iodide to introduce the azide group. In our initial attempt, we tested the influence of the solvent (Table 2, entries 1–3 and entries 6–7) and found that protic solvents, such as H2O and MeOH, led to degradation of product 7, while the use of aprotic solvents, such as acetone, DMF and MeCN resulted in a low yield of 7 (30%). Moreover, we found that heating the reaction only afforded a complex mixture (entries 4 and 8). An increase in the quantity of NaN₃ and reaction time did not improve the yield of this reaction (entry 5). In an attempt to increase the yield of 7, we treated iodo-morpholinone 5 with sodium azide in the presence of various additives (entries 9–11) and found that product 7 could be obtained from 5 in a very high yield (90%) in the presence of 18-crown-6. However, further investigation showed that, whereas increasing the amount of the latter reduces the reaction time, it did not give a better yield (entries 12 and 13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electro- ( \text{equiv} )</th>
<th>Solvent</th>
<th>Base (equiv)</th>
<th>Temp (^\circ\text{C} )</th>
<th>Additive (equiv)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>rt</td>
<td>–</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>NBS (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>50</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>ICl (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>–</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NIS (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>–</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>50</td>
<td>–</td>
<td>tracec</td>
</tr>
<tr>
<td>6</td>
<td>I₂ (2)</td>
<td>THF</td>
<td>Na₂CO₃ (3)</td>
<td>rt</td>
<td>–</td>
<td>b</td>
</tr>
<tr>
<td>7</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>NaH (1.5)</td>
<td>0</td>
<td>–</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>NaOH (3)</td>
<td>50</td>
<td>–</td>
<td>45</td>
</tr>
<tr>
<td>9</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>Et₃N (3)</td>
<td>rt</td>
<td>–</td>
<td>b</td>
</tr>
<tr>
<td>10</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>AgNO₃ (1)</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I₂ (2)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (3)</td>
<td>AgNO₃ (1.5)</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>I₂ (1.5)</td>
<td>CHCl₃</td>
<td>Na₂CO₃ (2)</td>
<td>AgNO₃ (1)</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography.
b Starting material.
c Complex mixture.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>NaN₃ (equiv)</th>
<th>Temp (^\circ\text{C} )</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>MeOH/H₂O</td>
<td>3</td>
<td>rt</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>MeOH</td>
<td>3</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>acetone</td>
<td>3</td>
<td>45</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>acetone</td>
<td>6</td>
<td>rt</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>DMF</td>
<td>3</td>
<td>rt</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>MeCN</td>
<td>3</td>
<td>rt</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>DMF</td>
<td>3</td>
<td>75</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>18-crown-6 (0.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>TBAI (0.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>TBAF (0.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>18-crown-6 (1)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>18-crown-6 (1.5)</td>
<td>acetone</td>
<td>3</td>
<td>rt</td>
<td>90</td>
</tr>
</tbody>
</table>

a Isolated yield.
b Degradation.
c Starting material 5 was recovered in 30% yield.
d 72 h (time of reaction).
e 18 h (time of reaction).
azide product under these conditions (in the presence of 18-crown-6), presumably because of the instability of the iodo-1,4-oxazepan-7-one 6.

In the next phase of the study, we wished to generate 1,2,3-triazole derivatives involving a 1,3-dipolar cycloaddition using azido morpholinone 7 as the starting material. Many protocols for the synthesis of 1,2,3-triazoles based on copper(I) catalysts have been reported. In our initial attempt, CuSO4·5H2O (10 mol%), was used as catalyst in the presence of sodium ascorbate (20 mol%) and phenylacetylene (1.5 equiv) in toluene/H2O (3:1) at room temperature; wherein 8a was obtained in a moderate yield (50%). An attempt to use copper(I) iodide under the same conditions was made, but again afforded moderate yields, as was the case with copper sulfate. We further examined the effect of solvents on the cycloaddition reaction (1:3 THF/H2O, toluene/H2O, DMF/H2O, CHCl3/H2O and CH2Cl2) and the best results were obtained when the reaction was carried out in either CH2Cl2 or CHCl3/H2O (Scheme 5). Under these conditions, compound 8a was obtained in good yield (90%).

Having established that morpholinone 5 can be transformed into 1,2,3-triazole derivatives in a two-step procedure, we decided to investigate the ‘one-pot’ cascade (Scheme 6) of the two previously defined steps (Scheme 4) and we found the presence of 18-crown-6 to be crucial for the azide substitution reaction to take place. In this context, iodomorpholinone 5 was subjected to the copper-catalyzed-multicomponent reaction in the presence of 18-crown-6 using phenylacetylene and sodium azide under the previously defined conditions. As expected, under these conditions (Scheme 6), the multicomponent click reaction worked well and the targeted 1,2,3-triazole 8a was obtained in 82% yield. It was found that 18-crown-6 is indispensable for this three-component reaction. This one-pot reaction led to the isolation of the desired product 8a with a similar yield to the two-step procedure (81%). To demonstrate the generality of this one-pot morpholinone-triazole synthesis reaction, a range of substituted 1,2,3-triazoles derivatives 8a–k were prepared in moderate to excellent yields by using the multicomponent reaction of iodomorpholinone 5 and sodium azide with various terminal alkynes.
In summary, we have developed an efficient and general methodology for the synthesis of novel six- and seven-membered iodo heterocycles through electrophilic iodo cyclization. We have also demonstrated that the resulting six-membered iodomorpholinone 5 afforded a novel series of heterocyclic derivatives based on morpholine and triazole heterocycles, prepared using a CuAAC one-pot procedure in the presence of 18-crown-6. Further investigations concerning the scope of applications are ongoing in our laboratory.

All reactions were carried out under an argon atmosphere in dried glassware. THF was distilled under argon from sodium benzenophene ketyl. Dimethylformamide was dried and freshly distilled from calcium hydride. Other chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Fluorochem or ABCR and used without further purification. Reactions were monitored by TLC with Merck silica gel 60 F254. TLC plates were visualized using UV light (254 nm) or staining with KMnO$_4$. Column chromatography was performed on silica gel (40–63 μm) using mixtures of EtOAc and petroleum ether (35–60 °C fraction) as eluent. $^1$H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using as internal deuterium lock the solvents CDCl$_3$ ($\delta$ 7.26 ppm), (CD$_3$)$_2$CO ($\delta$ 2.05 ppm) or (CD$_3$)$_2$SO ($\delta$ 2.54 ppm). Chemical shifts are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet and br = broad. Coupling constants ($J$) are reported in Hz. $^{13}$C NMR spectra were recorded at 75 MHz on the same instrument, using the solvent peak as reference. CDCl$_3$ ($\delta$ 77.16 ppm), (CD$_3$)$_2$CO ($\delta$ 28.95 ppm) or (CD$_3$)$_2$SO ($\delta$ 39.52 ppm). $^{19}$F NMR spectra were recorded at 282 MHz on the same instrument, using the CFCI as the internal reference ($\delta$ = 0.0 ppm). Mass spectra were obtained with a Hewlett Packard 5988A by direct inlet at 70 eV. HRMS were obtained with a LCMS-IT-TOF mass spectrometer under ESI. Infrared spectra were recorded on a PerkinElmer Spectrum One spectrophotometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima ($\lambda_{\text{max}}$) are quoted in wavenumbers. Melting points are uncorrected.

**Synthesis of 2-(Iodomethyl)-4-tosyl-1,4-oxazepan-7-one (6)**

In a round-bottom flask containing carboxylic acid 4 (1 equiv, 300 mg, 1.059 mmol) and CHCl$_3$ (25 mL) were added sodium carbonate (2 equiv, 224 mg, 2.12 mmol), iodine (1.5 equiv, 403 mg, 1.59 mmol) and silver nitrate (1.5 equiv, 180 mg, 1.06 mmol). The mixture was stirred for 2 h at r.t., quenched with a saturated solution of Na$_2$S$_2$O$_3$ (30 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over MgSO$_4$, filtered and evaporated under reduced pressure.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 7.68 (d, $J$ = 8.17 Hz, 2 H), 7.38 (d, $J$ = 8.17 Hz, 2 H), 4.48–4.54 (m, 1 H), 4.24–4.3 (dd, $J$ = 1.8 Hz, $J$ = 14.47 Hz, 1 H), 4.03–4.11 (m, 1 H), 3.38–3.41 (m, 2 H), 2.71–3.04 (m, 4 H), 2.47 (s, 3 H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 163.51, 145.29, 131.39, 130.43, 127.81, 77.27, 53.57, 46.71, 46.48, 21.5, 1.76.

HRMS (ESI): m/z [M + H]$^+$ calc for C$_{12}$H$_{15}$INO$_4$S: 395.99175; found: 395.99147.

**Synthesis of 6-(Azidomethyl)-4-tosylmorpholin-2-one (7)**

A mixture of the appropriate 6-(iodomethyl)-4-tosylmorpholin-2-one 5 (300 mg, 0.76 mmol), sodium azide (148 mg, 2.28 mmol), 18-crown-6 (100 mg, 0.38 mmol) and acetone (20 mL) was stirred at r.t. until completion of the reaction (TLC). The solvents were evaporated under reduced pressure, and the crude product was then poured into water, extracted with CH$_2$Cl$_2$ (3 × 40 mL), dried (MgSO$_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using PE/EtOAc (6:1) mixture as eluent.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.67 (d, $J$ = 8.3 Hz, 2 H), 7.40 (d, $J$ = 8.3 Hz, 2 H), 4.68–4.61 (m, 1 H), 4.11 (dd, $J$ = 1.1, 16.7 Hz, 1 H), 3.67–3.58 (m, 3 H), 3.53 (dd, $J$ = 4.4, 13.2 Hz), 2.94 (dd, $J$ = 8.6, 12.7 Hz, 1 H), 2.47 (s, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 163.52, 145.29, 131.34, 130.43, 130.28, 127.91, 76.77, 51.68, 46.97, 46.42, 21.71.

HRMS (ESI): m/z [M + H]$^+$ calc for C$_{13}$H$_{17}$INO$_4$S: 311.08805; found: 311.08011.

**Synthesis of Triazoles: General Procedures**

**Method A**

Finely powdered CuSO$_4$·5H$_2$O (16 mg, 0.10 mol%) and sodium ascorbate (26 mg, 0.20 mol%) were slowly added to a stirred solution of 6-(azidomethyl)-4-tosylmorpholin-2-one 7 (200 mg, 0.64 mmol) and terminal alkyne (0.96 mmol, 1.5 equiv) in H$_2$O/CHCl$_3$ (3:1 = 15 mL/5 mL) at 0–10 °C. The mixture was then allowed to reach r.t. and TLC monitoring was used to follow reaction progress. The mixture was filtered, concentrated and diluted with water (30 mL). The aqueous layer was extracted with CHCl$_3$ (3 × 20 mL), the combined organic layers were washed with H$_2$O and then with brine, dried over Na$_2$SO$_4$, filtered and concentrated under vacuum. The crude products were crystallized from various solvents or purified by flash chromatography over silica gel (elucent CHCl$_3$/MeOH = 88:12) to afford the desired pure triazole product.

**Method B**

6-(Iodomethyl)-4-tosylmorpholin-2-one 5 (789 mg, 2 mmol) was dissolved in H$_2$O/CHCl$_3$ (3:1 = 22.5 mL/7.5 mL). Sodium azide (390 mg, 6 mmol) and 18-crown-6 (264 mg, 1 mmol) were then added to the solution and the suspension was stirred for 30 min. The mixture was degassed at 0 °C, then the terminal alkyne (4.0 mmol, 2 equiv), sodi-
Yield: 675 mg (82%); white solid; mp 213–214 °C; crystallization (EtOH).

According to general procedure B, compound 8a was isolated after recrystallization (EtOH).

Yield: 675 mg (82%); white solid; mp 213–214 °C; crystallization (EtOH).

According to general procedure B, compound 8a was isolated after recrystallization (EtOH).

Yield: 675 mg (82%); white solid; mp 213–214 °C; crystallization (EtOH).

According to general procedure B, compound 8a was isolated after recrystallization (EtOH).

Yield: 716 mg (80%); white solid; mp 213–214 °C; crystallization (EtOH).

According to general procedure B, compound 8b was isolated after recrystallization (EtOH).

Yield: 681 mg (80%); white solid; mp 191–192 °C; \( R_f = 0.35 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8b was isolated after recrystallization (EtOH).

Yield: 681 mg (80%); white solid; mp 191–192 °C; \( R_f = 0.35 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8c was isolated after recrystallization (EtOH).

Yield: 680 mg (77%); white solid; mp 225–226 °C; \( R_f = 0.37 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8c was isolated after recrystallization (EtOH).

Yield: 716 mg (80%); white solid; mp 213–214 °C; \( R_f = 0.35 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8d was isolated after recrystallization (EtOH).

Yield: 533 mg (62%); white solid; mp 191–192 °C; \( R_f = 0.38 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8d was isolated after recrystallization (EtOH).

Yield: 533 mg (62%); white solid; mp 191–192 °C; \( R_f = 0.38 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8e was isolated after recrystallization (EtOH).

Yield: 705 mg (82%); white solid; mp 207–208 °C; \( R_f = 0.38 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8e was isolated after recrystallization (EtOH).

Yield: 705 mg (82%); white solid; mp 207–208 °C; \( R_f = 0.38 \) (EtOAc/PE = 4:1).

According to general procedure B, compound 8f was isolated after recrystallization (EtOH).

Yield: 716 mg (80%); white solid; mp 213–214 °C; \( R_f = 0.35 \) (EtOAc/PE = 4:1).
6-[(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)methyl]-4-tosylmorpholin-2-one (8h)

According to general procedure B, compound 8h was isolated after re-crystallization (EtOH).

Yield: 609 mg (67%); white solid; mp 237–238 °C; crystallization (EtOH).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): δ = 164.1, 161.78 (dd, J = 12.5, 247.3 Hz), 158.49 (dd, J = 12.7, 248.6 Hz), 144.41, 139.12 (d, J = 2.2 Hz), 131.70, 130.15, 128.50 (dd, J = 5.2, 9.7 Hz), 127.68, 124.41 (d, J = 11.1 Hz), 115.03 (dd, J = 3.75, 13.4 Hz), 112.30 (dd, J = 3.25, 21.3 Hz), 104.56 (t, J = 26 Hz), 75.79, 50.74, 46.51, 43.48, 20.99.

$^{10}$F NMR (282 MHz, DMSO-d$_6$): δ = −110.56 (d, J = 7.7 Hz), −110.35 (d, J = 7.7 Hz).

HRMS (ESI): m/z [M + H$^+$] calcd for C$_{13}$H$_{23}$N$_5$O$_4$: 377.12830; found: 377.12731.

$N$-Butyl-4-methyl-$N'$-(1-[6-oxo-4-tosylmorpholin-2-yl]methyl)-1H-1,2,3-triazol-4-yl)methyl]benzenesulfonylamide (8j)

According to general procedure B, compound 8j was isolated after recrystallization (EtOH).

Yield: 851 mg (74%); white solid; mp 179–180 °C; R$_f$ = 0.33 (EtOAc/PE = 4:1).

$^1$H NMR (300 MHz, DMSO-d$_6$): δ = 7.95 (s, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.66 (d, J = 8.2 Hz, 2 H), 7.48 (d, J = 8.1 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 4.93–4.87 (m, 1 H), 4.73–4.61 (m, 2 H), 4.37 (s, 2 H), 4.03 (d, J = 17.2 Hz, 1 H), 3.72 (dd, J = 2.9, 12.4 Hz, 1 H), 3.71 (d, J = 17.2 Hz, 1 H), 2.95–3.07 (m, 3 H), 2.42 (s, 3 H), 2.38 (s, 3 H), 1.40–1.30 (m, 2 H), 1.15–1.07 (m, 2 H), 0.74 (t, J = 7.27 Hz, 3 H).

$^{13}$C NMR (75 MHz, DMSO-d$_6$): δ = 163.98, 144.48, 143.08, 142.94, 136.29, 131.7, 130.21, 129.72, 127.68, 126.93, 124.89, 75.91, 50.54, 47.32, 46.84, 43.52, 42.33, 29.54, 21.04, 20.94, 19.05, 13.39.

HRMS (ESI): m/z [M + H$^+$] calcd for C$_{23}$H$_{30}$N$_5$O$_4$S$_2$: 576.19450; found: 576.19292.

$N$-Allyl-4-methyl-$N'$-[1-[6-oxo-4-tosylmorpholin-2-yl]methyl]-1H-1,2,3-triazol-4-yl)methyl]benzenesulfonylamide (8k)

According to general procedure B, compound 8k was isolated after flash chromatography.

Yield: 771 mg (60%); white solid; mp 157–158 °C; R$_f$ = 0.35 (EtOAc/PE = 4:1).

$^1$H NMR (300 MHz, acetone-d$_6$): δ = 7.83 (s, 1 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 7.37 (d, J = 8.4 Hz, 2 H), 5.60 (ddt, J = 6.3, 10.2, 17.1 Hz, 1 H), 5.15 (dq, J = 1.5, 17.1 Hz, 1 H), 5.05 (dq, J = 1.6, 10.2 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.84–4.71 (m, 2 H), 4.43 (s, 2 H), 4.03 (d, J = 17.3 Hz, 2 H), 3.84–3.76 (m, 2 H), 3.10 (dd, J = 8.3, 12.8 Hz, 2 H), 2.42 (s, 3 H), 2.39 (s, 3 H).

$^{13}$C NMR (75 MHz, acetone-d$_6$): δ = 164.27, 145.67, 144.29, 138.44, 133.51, 131.1, 130.62, 128.80, 128.18, 119.14, 77.28, 70.82, 51.93, 50.73, 47.58, 44.95, 42.48, 21.85, 21.49.

HRMS (ESI): m/z [M + H$^+$] calcd for C$_{20}$H$_{22}$N$_5$O$_4$: 580.16320; found: 560.16186.

Acknowledgment

We acknowledge Dr. Frédéric Montigny (Tours University) for recording mass spectra and HRMS and Dr. Karen Wright (Versailles University) for proof-reading the manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610399.

References


