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

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I. General remarks

General Methods: All reactions were carried out under argon atmosphere in dried glassware. THF was distilled under argon from sodium using benzophenone as indicator. Dimethylformamide was dried and freshly distilled from calcium hydride. Chemicals were purchased from commercial sources (Sigma–Aldrich, Alfa Aesar, Fluorochem or ABCR) and used without further purification.

Reactions were monitored by TLC with Merck® Silica gel 60 F254. The developed TLC plates were visualized by using UV light (254 nm) or KMnO4. Column chromatography was performed on silica gel (40-63 µm) using various mixtures of EtOAc and petroleum ether (35-60 °C fraction) as eluent. 1H NMR spectra were recorded on a Bruker® Avance 300 (300 MHz) NMR spectrometer, using as internal deuterium lock the solvents CDCl3 (δ 7.26), (CD3)2CO (δ 2.05) or (CD3)2SO (δ 2.54). Chemical shifts are quoted in ppm (δH, δC). Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet and br = broad. Coupling constants (J) are reported in Hz. 13C NMR was recorded at 75 MHz on the same instrument, using the solvent peak at as reference CDCl3 (δ 77.16), (CD3)2CO (δ 29.85) or (CD3)2SO (δ 39.52). 19F NMR was recorded at 282 MHz on the same instrument, using the CFCl3 as internal reference (δ 0.0). Mass spectra were obtained on a Hewlett Packard (engine 5988A) by direct inlet at 70eV. HRMS was obtained with a LCMS-IT-TOF mass spectrometer under conditions of ESI. Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima (νmax) are quoted in wavenumbers (cm⁻¹). Melting points were uncorrected.
II. Spectra data for compounds 1, 2, 3 and 4

Ethyl N-allyl-N-tosylglycinate (1)
Synthesized as described above and characterized according to NMR comparison\(^1\)
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.73\) (d, \(J = 8.2\) Hz, 1 H), 7.30 (d, \(J = 8.2\) Hz, 1 H), 5.69 (ddt, \(J = 6.6, 10.6, 16.6\) Hz, 1 H), 5.21-5.13 (m, 2 H), 4.08 (q, \(J = 7.1\) Hz, 2 H), 4.01 (s, 2 H), 3.89 (d, \(J = 6.5\) Hz, 2 H), 2.42 (s, 3 H), 1.21 (t, \(J = 7.1\) Hz, 3 H).

2-(N-Allyl-N-tosylamino)acetic acid (2)
Synthesized as described above and characterized according to NMR comparison\(^2\)
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.40\) (s, 1 H), 7.72 (d, \(J = 8.1\) Hz, 1 H), 7.30 (d, \(J = 8.1\) Hz, 1 H), 5.65 (ddt, \(J = 6.5, 10.3, 16.8\) Hz, 1 H), 5.22-5.15 (m, 2 H), 4.02 (s, 2 H), 3.88 (d, \(J = 6.5\) Hz, 2 H), 2.43 (s, 3 H).

Typical procedure for synthesis of compound 3 by using Kim’s method\(^3\)

To a magnetically stirred solution of \(N\)-allyl-4-methylbenzenesulfonamide (1 mmol) and methyl acrylate (1.5 mmol, 1.5 equiv.) in CH\(_3\)CN (0.5 ml) was added DBU (0.5 mmol, 0.5 equiv.) at room temperature. After 6 h, the mixture was concentrated through vacuum evaporation. The

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resulting residue was purified by silica gel column chromatography (EP/EtOAc = 4:1), and the pure methyl 3-((N-allyl-4-methylphenyl)sulfonamido)propanoate was isolated in 88% yield.

**Methyl 3-((N-allyl-4-methylphenyl)sulfonamido)propanoate (3):**

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.70 (d, $J$ = 8.3 Hz, 1 H), 7.30 (d, $J$ = 8.3 Hz, 1 H), 5.64 (ddt, $J$ = 6.4, 10.2, 16.9 Hz, 1 H), 5.23-5.13 (m, 2 H), 3.80 (dt, $J$ = 1.1, 6.4 Hz, 2 H), 3.66 (s, 3 H), 3.39 (t, $J$ = 7.4 Hz, 2 H), 2.64 (t, $J$ = 7.4 Hz, 2 H), 2.43 (s, 3 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 171.7, 143.5, 136.5, 132.9, 129.8, 127.1, 119.2, 51.7, 51.5, 43.1, 34.1, 21.5.

HRMS (ESI): calcd for C$_{14}$H$_{20}$NO$_4$S [M+H]$^+$ 298.1113; found 298.1119.

3-((N-allyl-4-methylphenyl)sulfonamido)propanoic acid (4)

Synthesized as described above and characterized according to NMR comparison$^4$

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.20 (s, 1 H), 7.70 (d, $J$ = 8.3 Hz, 1 H), 7.31 (d, $J$ = 8.3 Hz, 1 H), 5.64 (ddt, $J$ = 6.5, 10.1, 17.1 Hz, 1 H), 5.23-5.14 (m, 2 H), 3.80 (dt, $J$ = 1.1, 6.5 Hz, 2 H), 3.38 (t, $J$ = 7.3 Hz, 2 H), 2.69 (t, $J$ = 7.3 Hz, 2 H), 2.43 (s, 3 H).

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III. Copies of $^1$H and $^{13}$C NMR spectra for all products

Methyl 3-(N-allyl-4-methylphenylsulfonamido)propanoate (3)
6-(Iodomethyl)-4-tosylmorpholin-2-one (5)
6-(Azidomethyl)-4-tosylmorpholin-2-one (7)
6-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8a)
6-((4-(p-Tolyl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8b)
6-((4-(4-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8c)
6-((4-(2-Fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8d)
6-((4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8c)
6-((4-(2,4-Difluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8f)
6-((4-(Pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8g)
6-((4-(4-(Dimethylamino)phenyl)-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8h)
6-((4-Cyclopropyl-1H-1,2,3-triazol-1-yl)methyl)-4-tosylmorpholin-2-one (8i)
$N$-Butyl-4-methyl-$N$-((6-oxo-tosylmorpholin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)benzenesulfonamide (8j)
N- Allyl-4-methyl-N-{1-((6-oxo-4-tosylmorpholin-2-yl)methyl)-1H-1,2,3-triazol-4-yl}benzenesulfonamide (8k)
2-(Iodomethyl)-4-tosyl-1,4-oxazepan-7-one (6)