A Synthetic Route to [1,2,4]Triazolo[1,5-*a*][4,1]benzoxazepines

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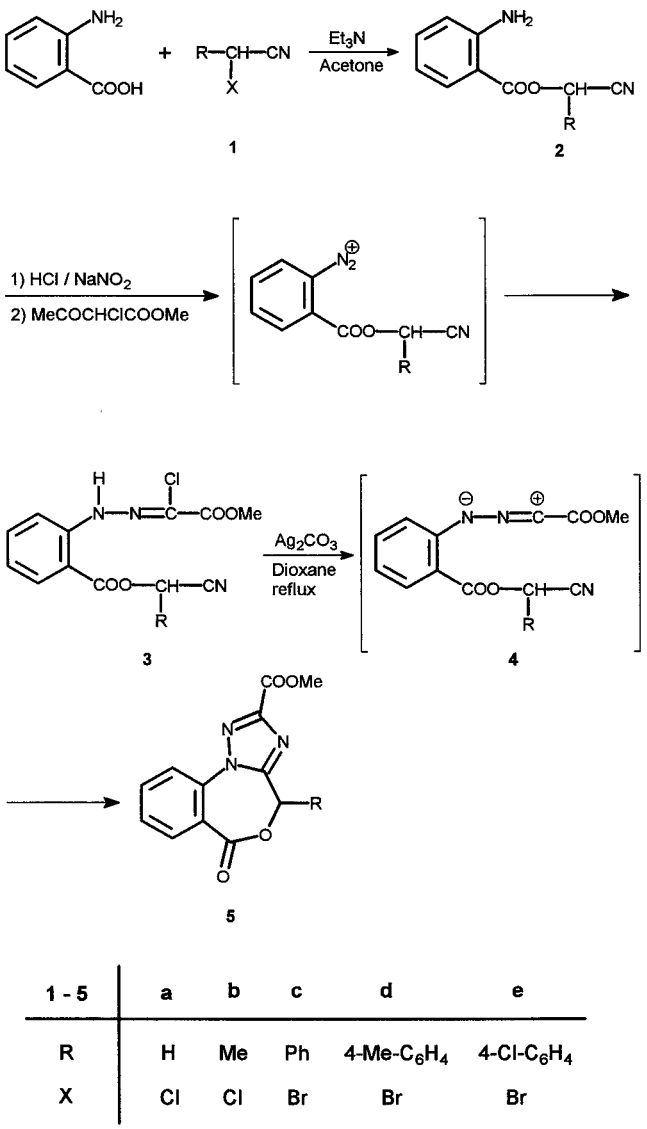
A reaction sequence leading to the new title compounds is described, the key step of which is an intramolecular cycloaddition of nitrilimine to a nitrile group.

The synthetic importance of intramolecular 1,3-dipolar cycloadditions is increasingly recognized.[1,2] In continuation of our research line dealing with the construction of heterocyclic systems by means of the intramolecular nitrilimine cycloaddition methodology,[3-7] we have developed a synthetic entry to the hitherto unknown [1,2,4]triazolo[1,5-*a*][4,1]benzoxazepines **5**.

As illustrated in the Scheme, our sequence started from the reaction of the trivial anthranilic acid with a series of α-halonitriles **1**. The resulting ortho-substituted anilines **2** were submitted to diazotization and coupling with methyl 2-chloroacetoacetate to afford the hydrazonyl chlorides **3**. Treatment of the latter with silver carbonate in refluxing dioxane generated the transient nitrilimines **4**, whose intramolecular cycloaddition to the nitrile group produced the desired tricyclic compounds **5**.

The extent of the intramolecular cycloaddition may appear *prima facie* disappointing, however, it is to be stressed that nitriles are usually very poor dipolarophiles toward nitrilimines[8] and only entropic factors due to the intramolecularity can force the cycloaddition onto the C≡N functionality.



1 - 5	a	b	c	d	e
R	H	Me	Ph	4-Me-C_6H_4	4-Cl-C_6H_4
X	Cl	Cl	Br	Br	Br

Scheme

Melting points were determined on a Büchi apparatus and are not corrected. IR spectra were recorded on a FT-IR Perkin-Elmer 1725 X spectrophotometer. Mass spectra were taken with a WG – 70EQ apparatus. ^{1}H NMR spectra were obtained on a Bruker 300 MHz apparatus; chemical shifts are given as ppm from TMS.

Compound **1c** was prepared according to the literature.[9] Compounds **1a, b** are commercially available.

2-Bromo-2-(4-methylphenyl)acetonitrile (1d):
To a solution of 2-(4-methylphenyl)acetonitrile (5.00 g, 38.1 mmol) in CCl_4 (30 mL) warmed to 70 °C, was added dropwise Br_2 (6.70 g, 41.9 mmol) under vigorous stirring. The mixture was refluxed for 3 h and then allowed to stand overnight at r.t. After removal of the solvent, the residue was distilled under reduced pressure giving **1d**; yield: 3.20 g (40%); bp 100 °C/ 6 Torr.

Table 1. Preparation and Characterization of Compounds **2**

Product[a]	Yield (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	MS (70 eV) *m/z* (M$^+$)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
2a	48	64	3470, 3380, 2240, 1700	176	4.89 (2H, s), 5.73 (2H, br s), 6.62–7.81 (4H, m)
2b	16	61	3480, 3360, 2250, 1700	190	1.76 (3H, d, *J* = 6.9), 5.56 (1H, q, *J* = 6.9), 5.73 (2H, br s), 6.63–7.83 (4H, m)
2c	58	102	3500, 3390, 2240, 1700	252	5.73 (2H, br s), 6.61 (1H, s), 6.63–7.84 (9H, m)
2d	25	98	3480, 3370, 2240, 1710	266	2.40 (3H, s), 5.71 (2H, br s), 6.56 (1H, s), 6.59–7.82 (8H, m)
2e	53	126	3480, 3380, 2250, 1700	286	5.74 (2H, br s), 6.58 (1H, s), 6.61–7.81 (8H, m)

[a] All compounds gave satisfactory microanalyses: C ± 0.18, H ± 0.16, Cl ± 0.17, N ± 0.15.

Table 2. Preparation and Characterization of Compounds **3**

Product[a]	Yield (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	MS (70 eV) m/z (M^+)	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	61	135	3220, 2230, 1730, 1710	281	3.92 (3H, s), 4.96 (2H, s), 7.00–7.98 (4H, m), 11.50 (1H, br s)
3b	93	137	3230, 2240, 1740, 1700	295	1.82 (3H, d, J = 6.9), 3.91 (3H, s), 5.65 (1H, q, J = 6.9), 7.02–7.98 (4H, m), 11.52 (1H, br s)
3c	63	139	3230, 2250, 1730, 1700	357	3.92 (3H, s), 6.77 (1H, s), 7.01–7.99 (9H, m), 11.53 (1H, br s)
3d	67	125	3240, 2240, 1720, 1700	371	2.40 (3H, s), 3.94 (3H, s), 6.63 (1H, s), 7.00–7.97 (8H, m), 11.46 (1H, br s)
3e	50	115	3240, 2250, 1730, 1705	391	3.94 (3H, s), 6.64 (1H, s), 7.01–7.95 (8H, m), 11.40 (1H, br s)

[a] All compounds gave satisfactory microanalyses: C ± 0.17, H ± 0.17, Cl ± 0.19, N ± 0.16.

Table 3. Preparation and Characterization of Compounds **5**

Product[a]	Time (h)	Eluent	Yield (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	MS (70 eV) m/z (M^+)	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	3	CH_2Cl_2/EtOAc (3 : 1)	32	189	1750, 1740	245	4.06 (3H, s), 5.34 (2H, s), 7.63–8.16 (4H, m)
5b	3	CH_2Cl_2/EtOAc (3 : 1)	18	186	1760, 1730	259	2.04 (3H, d, J = 6.3), 4.05 (3H, s), 5.37 (1H, q, J = 6.3), 7.61–8.15 (4H, m)
5c	2	CH_2Cl_2/EtOAc (5 : 1)	4	215	1750, 1730	321	4.04 (3H, s), 6.44 (1H, s), 7.37–7.42 (5H, m), 7.56–8.09 (4H, m)
5d	2.5	LP[b]/EtOAc (2 : 1)	28	195	1760, 1740	335	2.35 (3H, s), 4.05 (3H, s), 6.42 (1H, s), 7.17–7.31 (4H, m), 7.55–8.08 (4H, m)
5e	2	LP[b]/EtOAc (2 : 1)	7	191	1750, 1730	355	4.04 (3H, s), 6.35 (1H, s), 7.37–7.45 (4H, m), 7.59–8.11 (4H, m)

[a] All compounds gave satisfactory microanalyses: C ± 0.16, H ± 0.17, Cl ± 0.18, N ± 0.14.
[b] LP = light petroleum, bp 40–60 °C.

IR (neat): $\nu = 2230\ cm^{-1}$.

^1H NMR ($CDCl_3$): δ = 2.37 (3H, s), 5.48 (1H, s), 7.15–7.50 (4H, m).

MS (EI): m/z = 210 (M^+).

2-Bromo-2-(4-chlorophenyl)acetonitrile (1e):
To a solution of 2-(4-chlorophenyl)acetonitrile (5.00 g, 33.0 mmol) in CCl_4 (20 mL) warmed to 70 °C was added dropwise a solution of Br_2 (5.80 g, 36.3 mmol) in CCl_4 (10 mL) under stirring. The mixture was refluxed for 5 h and then allowed to stand overnight at r.t. The solvent was removed under reduced pressure and the residue was purified by crystallisation from diisopropyl ether to afford **1e**; yield: 5.48 g (72%); mp 187 °C.

IR (Nujol): $\nu = 2230\ cm^{-1}$.

^1H NMR ($CDCl_3$): δ = 5.50 (1H, s), 7.28–7.60 (4H, m).

MS (EI): m/z = 235 (M^+).

Anthranilates 2a–e; General Procedure:
A solution of anthranilic acid (10.00 g, 73.0 mmol) in anhydr. acetone (150 mL) was treated with Et_3N (7.37 g, 73.0 mmol). A solution of the halide **1** (75 mmol) in anhydr. acetone (20 mL) was added and the mixture was reacted for 24 h at r.t. The undissolved material was filtered off, the solvent was evaporated and the residue was crystallised from diisopropyl ether affording the anthranilates **2** (Table 1).

Hydrazonyl Chlorides 3a–e; General Procedure:
$NaNO_2$ (1.52 g, 22.0 mmol) was added portionwise to a solution of **2** (15.0 mmol) in 2 N aq HCl (20 mL) and glacial AcOH (10 mL) under vigorous stirring and cooling at 0 °C. After 20 min the pH of the cold mixture was adjusted to 5 with NaOAc and then methyl 2-chloroacetoacetate (2.25 g, 15.0 mmol) was added whilst it was cooled and stirred. The mixture was stirred at r.t. for 6 h and extracted with Et_2O. The organic layer was washed with 5% aq $NaHCO_3$, dried and evaporated. Crystallisation from diisopropyl ether gave the hydrazonyl chlorides **3** (Table 2).

[1,2,4]Triazolo[1,5-α][4,1]benzoxazepines 5a–e; General Procedure:
A solution of **3** (5.0 mmol) in anhydr. dioxane (165 mL) was treated with Ag_2CO_3 (2.76 g, 10 mmol) and the mixture was refluxed under stirring in the dark for the time indicated in Table 3. The undissolved material was filtered off, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column to give the cycloadducts **5** (Table 3).

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