

CONSTRUCTION OF THE PYRAZOLO[1,5-a][4,1]BENZOTHAZEPINE SYSTEM BY INTRAMOLECULAR NITRILIMINE CYCLOADDITION

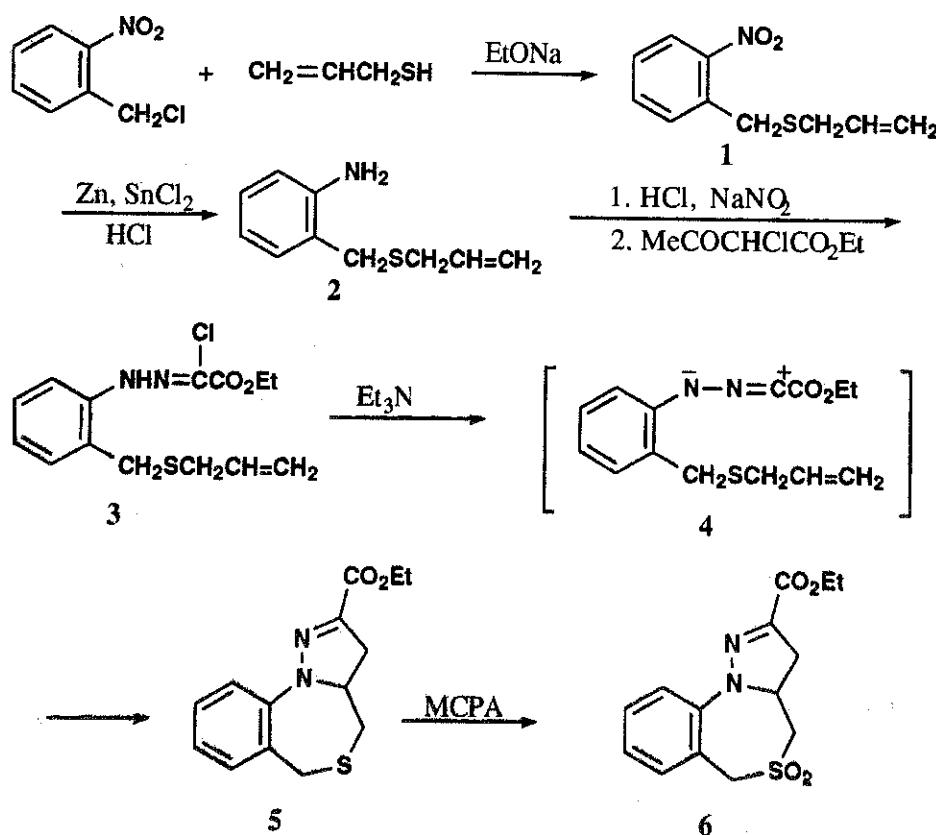
Submitted by
(1/21/92)

Gianluigi Brogini, Luca Bruché and Gaetano Zecchi*

*Dipartimento di Chimica Organica e Industriale Università di Milano
Via Golgi 19, 20133 Milano, ITALY*

Within our research framework aimed at the synthesis of fused-ring heterocycles *via* intramolecular cycloaddition of functionalized nitrile imines,¹⁻⁴ we explored the possibility of applying this strategy to the construction of the unreported pyrazolo[1,5-a][4,1]benzothiazepine system.

Starting from the commercially available 2-nitrobenzyl chloride and allyl mercaptan, we prepared nitro derivative **1**, which was then reduced to the corresponding aniline **2** with stannous chloride. Diazotization of **2** and subsequent coupling with ethyl 2-chloroacetoacetate afforded the hydrazonyl chloride **3**. The reaction of **3** with an excess of triethylamine in boiling benzene gave the tricyclic compound **5** resulting from the intramolecular cycloaddition of the transient nitrilimine **4**. Treatment of **5** with 3-chloroperbenzoic acid led to the corresponding *S,S*-dioxide **6**. It is worthwhile to notice that, while intramolecular nitrilimine cycloadditions have been exploited to prepare five/five- and five/six-membered annulated heterocycles,^{1-3,5} only a few examples deal with the formation of five/seven-membered systems.⁴



EXPERIMENTAL SECTION

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1725X FT spectrophotometer. NMR spectra were recorded on Varian EM-390 and Varian XL-200 instruments; chemical shifts are given in δ ppm from SiMe_4 . Mass spectra were measured on a WG-70EQ apparatus.

3-(2-Nitrobenzylthio)propene (1).—A solution of 2-nitrobenzyl chloride (5.1 g, 30 mmol) and allyl mercaptan (2.4 g, 30 mmol) in ethanol (100 mL) was added dropwise to 0.5 M sodium ethoxide in ethanol (55 mL). The mixture was stirred overnight at room temperature; the undissolved material was filtered off, and the solvent was evaporated under reduced pressure. The residue was taken up with dichloromethane, washed with 5% aqueous NaOH, dried over Na_2SO_4 , and evaporated. The oily residue was practically pure 1 (5.7 g, 90%). ^1H NMR (90 MHz, CDCl_3): δ 3.10 (2H, d, $J=7$), 4.05 (2H, s), 4.90–5.10 (2H, m), 5.50–6.00 (1H, m), 7.20–8.00 (4H, m); MS (EI, 70 eV): m/z 209 (M^+).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_2\text{S}$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.56; H, 5.49; N, 6.54.

3-(2-Aminobenzylthio)propene (2).—A solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (5.7 g, 25 mmol) in 35% aqueous HCl (100 mL) was added dropwise to a stirred solution of 1 (5.2 g, 25 mmol) in acetic acid (100 mL) at 15° . Zinc powder (16 g, 0.25 mol) was then added portionwise under vigorous stirring and cooling. After 2 hrs, the undissolved material was filtered off and the solution was adjusted to pH 5 with concentrated ammonia. The solvent was partly removed under reduced pressure and the residue was alkalinized and extracted with dichloromethane. The organic solution was dried over Na_2SO_4 and evaporated. Distillation of the residue gave amine 2, bp. $155\text{--}160^\circ/0.2$ torr (3.0 g, 67%). ^1H NMR (90 MHz, CDCl_3): δ 3.08 (2H, d, $J=7$), 3.69 (2H, s), 4.00 (2H, br s), 5.00–5.20 (2H, m), 5.50–6.00 (1H, m), 6.50–7.20 (4H, m). MS (EI, 70 eV): m/z 179 (M^+).

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{NS}$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.14; H, 7.52; N, 7.71.

Ethyl 2-[2-(Allylthiomethyl)phenylhydrazono]-2-chloroacetate (3).—A solution of 2 (3.6 g, 20 mmol) in 2 N aqueous HCl (30 mL) was cooled at 0° and treated with a solution of ethyl 2-chloroacetate (10.8 g, 50 mmol) in methanol (30 mL). A solution of NaNO_2 (1.6 g, 22 mmol) in water (20 mL) was then added dropwise under vigorous stirring and ice-cooling. The mixture was adjusted to pH 5 with AcONa, stirred at room temperature for 3 hrs, and extracted with dichloromethane. The organic solution was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel column with light petroleum-ethyl acetate (4:1) as eluent to give compound 3, mp. $39\text{--}41^\circ$ (from pentane) (2.9 g, 46%). IR (Nujol): $3240, 1725\text{ cm}^{-1}$; ^1H NMR (90 MHz, CDCl_3): δ 1.43 (3H, t, $J=7$), 3.10 (2H, d, $J=7$), 3.71 (2H, s), 4.42 (2H, q, $J=7$), 4.90–5.20 (2H, m), 5.50–6.00 (1H, m), 6.80–7.70 (4H, m), 9.50 (1H, br s); MS (EI, 70 eV): m/z 312 (M^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S}$: C, 53.75; H, 5.48; N, 8.96. Found: C, 53.90; H, 5.72; N, 8.72.

2-Ethoxycarbonyl-3,3a-dihydro-4H,6H-pyrazolo[1,5-a][4,1]benzothiazepine (5).—A solution of 3 (1.43 g, 4.6 mmol) and triethylamine (2.3 g, 23 mmol) in benzene (230 mL) was refluxed for 12 hrs. The resulting mixture was washed with aqueous HCl, dried over Na_2SO_4 , and evaporated. The residue

was taken up with diisopropyl ether and filtered to afford practically pure 5, mp. 106-107° (from hexane-benzene) (0.49 g, 39%). IR (Nujol): 1715 cm^{-1} ; ^1H NMR (200 MHz, C_6D_6): δ 1.42 (3H, t, J 7), 2.70-4.10 (7H, overlapping), 4.35 (2H, q, J 7), 7.00-7.40 (4H, m); MS (EI, 70 eV): m/z 276 (M^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 60.84; H, 5.84; N, 10.14. Found: C, 60.68; H, 6.01; N, 10.03.

2-Ethoxycarbonyl-3,3a-dihydro-4H,6H-pyrazolo[1,5-a][4,1]benzothiazepine 5,5-Dioxide (6). A solution of 5 (415 g, 154 mmol) and 3-chloroperbenzoic acid (0.28 g, 1.6 mmol) in dichloromethane (20 mL) was stirred at room temperature for 3 hrs. After filtration, the solution was washed with aqueous NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_5$, dried over Na_2SO_4 , and evaporated. Recrystallization of the residue from ethanol gave compound 6, mp. 142-143° (87 mg, 51%). IR (Nujol): 1690 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.41 (3H, t, J 7), 2.85 (1H, dd, J 18 and 11), 3.30-4.20 (5H, overlapping), 4.35 (2H, q, J 7), 4.52 (1H, d, J 15), 7.00-7.40 (4H, m); MS (EI, 70 eV): m/z 308 (M^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C, 54.53; H, 5.23; N, 9.09. Found: C, 54.71; H, 5.47; N, 8.98.

Acknowledgements. Financial support from MURST (Rome) is gratefully acknowledged.

REFERENCES

1. L. Garanti, A. Sala and G. Zecchi, *Synthesis*, 666 (1975); L. Garanti, A. Sala and G. Zecchi, *Synth. Commun.*, 6, 269 (1976).
2. L. Garanti, A. Sala and G. Zecchi, *J. Org. Chem.*, 42, 1389 (1977).
3. L. Bruché and G. Zecchi, *J. Chem. Res.*, 210 (1986); L. Bruché and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 399 (1987).
4. L. Bruché and G. Zecchi, *Tetrahedron*, 45, 7427 (1989).
5. A. Padwa, "1,3-Dipolar Cycloaddition Chemistry", Wiley-Interscience, New York, NY, 1984, Vol. 2, Ch. 12.
