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A Facile Synthesis of Flumazenil Analogues

Gianluigi Broggini,*[a] Giorgio Molteni,[b] Alberto Terraneo[b] and Gaetano Zecchi[a]

[a] Università dell'Insubria, Dipartimento di Scienze Chimiche, Fisiche e Matematiche, via Lucini 3, 22100 Como, Italy

[b] Università di Milano, Dipartimento di Chimica Organica e Industriale, via Golgi 19, 20133 Milano, Italy

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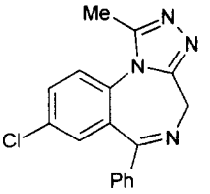
Abstract: A number of 8-substituted 5-methyl[1,2,3]triazolo[1,5-*a*][1,4] benzodiazepin-6(4*H*)-ones (**6**) were synthesised in a concise and efficient way starting from isatoic anhydrides and exploiting an intramolecular azide cycloaddition.

1,4-Benzodiazepines fused to a five-membered heterocycle occupy a prominent place among drugs for the treatment of CNS disturbances.[1-5] For instance, alprazolam **1** is a common anxiolytic agent,[6] while flumazenil **2** belongs to the family of cognition enhancers.[7]



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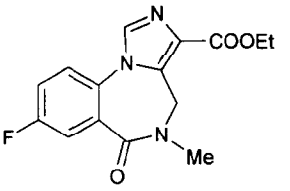

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Within our research into heterocyclic syntheses by means of intramolecular 1,3-dipolar cycloadditions of the azido group,[8,9] we have developed a facile entry to a series of 8-substituted 5-methyl-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones **6**, the structure of which is closely related to that of flumazenil.

Results and Discussion

Our synthetic approach started from the reaction of 5-substitued isatoic anhydrides **3** with the commercially available methylpropargylamine (Scheme 1). The reaction was carried out in boiling dioxane in the case of **3a** and in boiling DMF in the case of the less reactive substrates **3b-d**, to give the anthranilamides **4** in 44-54% yield. These were subjected to diazotization and subsequent reaction of the intermediate diazonium salts with sodium azide. The expected azides **5** were not isolable as intramolecular cycloaddition onto the acetylenic bond occurred spontaneously *in situ*, and simple evaporation of the solvent led to the final targets **6**. The overall yields of 41-55% in this cascade-type reaction sequence from **4** are preparatively useful. Further in order to widen the variety of the targets, the nitro derivate **6d** was converted into the corresponding amino derivative **6e** *via* catalytic hydrogenation.

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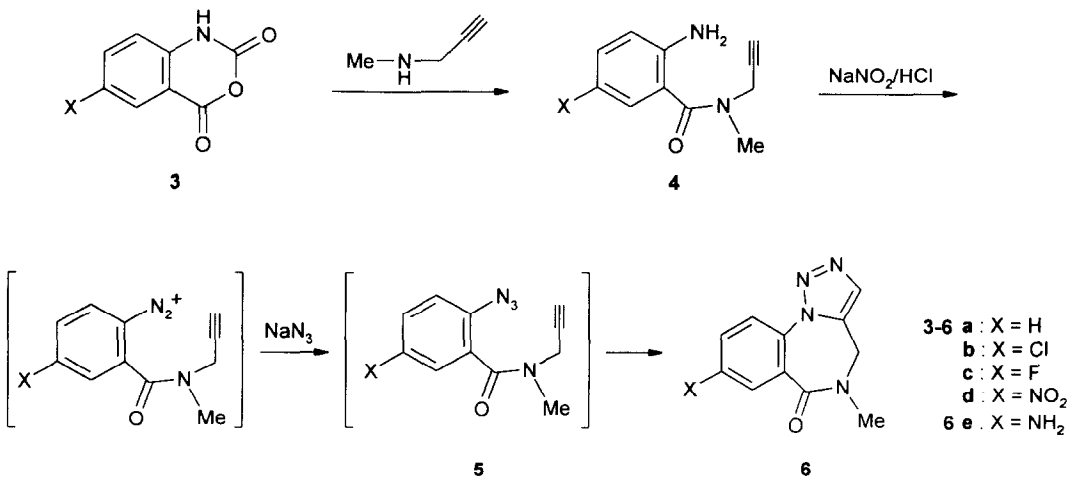
Scheme 1



The toxicological and pharmacological properties of the tricyclic compounds **6a-e** are under evaluation.

Experimental Section

M.p. were determined on a Büchi apparatus and are uncorrected. IR Spectra were recorded on a FT-IR Perkin-Elmer 1725X spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken using a Bruker 300 MHz apparatus; chemical shifts are given in ppm from $SiMe_4$, with coupling constants in Hz. Mass spectra were determined with a VG-70EQ apparatus.

Compounds **3a,b** were commercially available. Compounds **3c**[10] and **3d**[11] were prepared according to literature methods.

2-Amino-*N*-methyl-*N*-(prop-2-ynyl)benzamide 4a. *N*-Methylpropargylamine (200 mg, 2.9 mmol) was added to a solution of **3a** (315 mg, 1.9 mmol) in dioxane (10 mL). The mixture was heated at reflux for 3 h, then poured in ice/water (50 mL), adjusted to pH 9 with 5% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed on silica with chloroform/methanol 10:1 as eluent to give **4a** (195 mg, 54%). Oil; ^{1}H-NMR ($CDCl_3$) δ 2.31 (1H, t, *J* 2.4), 3.09 (3H, s), 4.19 (2H, d, *J* 2.4), 4.40 (2H, br s, missing after deuteriation), 6.71 (1H, d, *J* 7.7), 6.73 (1H, dd, *J* 7.4, 7.7), 7.14-7.24 (2H, m); IR (nujol) 1620, 2120, 3280, 3350, 3450 cm^{-1}; MS *m/z* 188 (M^+); Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.3; H, 6.48; N, 15.01.

General procedure for preparation of anthranilamides 4b-d. *N*-Methylpropargylamine (3.6 mmol) was added to a solution of **3b-d** (1.6 mmol) in DMF (8 mL). The mixture was heated at reflux for 3 h, then poured in ice/water (50 mL), adjusted to pH 9 with 5% NaOH and extracted with Et_2O. The organic layer was dried

over Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed on silica with chloroform/methanol 10:1 as eluent for **b-c** and diethyl ether/light petroleum 10:1 for **c**, giving the pure products **4b-d**.

4b: (53%). Oil; ^{1}H-NMR ($CDCl_3$) δ 2.32 (1H, t, *J* 2.3), 3.10 (3H, s), 4.19 (2H, d, *J* 2.3), 4.36 (2H, br s, missing after deuteriation), 6.64 (1H, d, *J* 8.6), 7.11 (1H, dd, *J* 2.4, 8.6), 7.16 (1H, d, *J* 2.4); IR (nujol) 1620, 2110, 3290, 3350, 3460 cm^{-1}; MS *m/z* 222 (M^+); Anal. Calcd. for $C_{11}H_{11}ClN_2O$; C, 59.33; H, 4.98; N, 12.58. Found: C, 59.26; H, 5.14; N, 12.53.

4c: (50%). Oil; ^{1}H-NMR ($CDCl_3$) δ 2.31 (1H, t, *J* 2.3), 3.10 (3H, s), 4.09 (4H, overlapping; after deuteriation: d, *J* 2.3), 6.66 (1H, dd, *J* 4.5, 9.2), 6.88-6.94 (2H, m); IR (nujol) 1625, 2120, 3295, 3350, 3450 cm^{-1}; MS: *m/z* 206 (M^+); Anal. Calcd. for $C_{11}H_{11}FN_2O$: C, 64.07; H, 5.38; N, 13.58. Found: C, 64.11; H, 5.47; N, 13.48.

4d: (44%). Oil; ^{1}H-NMR ($CDCl_3$) δ 2.39 (1H, t, *J* 2.3), 3.16 (3H, s), 4.24 (2H, d, *J* 2.3), 5.38 (2H, br s, missing after deuteriation), 6.72 (1H, d, *J* 9.0), 8.08 (1H, dd, *J* 2.6, 9.0), 8.21 (1H, d, *J* 2.6); IR (nujol) 1620, 2110, 3260, 3390, 3490 cm^{-1}; MS *m/z* 233 (M^+); Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.74; H, 4.91; N, 18.13.

General procedure for preparation of 5-methyl[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones 6a-d. $NaNO_2$ (1.2 mmol) was added portionwise to a solution of **4a-d** (0.6 mmol) in 1N aq HCl (4 mL) and glacial AcOH (7 mL) under stirring and cooling at 0 °C. After stirring for 40 min, the mixture was treated with cold Et_2O (16 mL) and NaN_3 (3.5 mmol) was added portionwise under vigorous stirring and ice-cooling for 3 h. The organic layer was separated, washed with aq $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **6a-d**.

6a: (41%). M.p. 169-171 °C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 3.21 (3H, s), 4.42 (2H, s), 7.55 (1H, ddd, *J* 1.2, 7.7, 7.8), 7.68 (1H, ddd, *J* 1.5, 7.6, 7.7), 7.74 (1H, s), 7.98 (1H, dd, *J* 1.2, 7.6), 8.07 (1H, dd, *J* 1.5, 7.8); ^{13}C-NMR ($CDCl_3$) δ 36.56 (q), 42.15 (t), 122.92 (d), 127.65 (s), 129.48 (d), 131.01 (d), 132.65 (d), 133.02 (s), 133.22 (d), 134.73 (s), 166.72 (s); IR (nujol) 1645 cm^{-1}; MS *m/z* 214 (35, M^+), 186 (44), 185 (58), 143 (73), 115 (100%); Anal. Calcd. for $C_{11}H_{10}N_4O$; C, 61.67; H, 4.71; N, 26.15. Found: C, 61.62; H, 4.84; N, 26.23.

6b: (55%). M.p. 146-148 °C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 3.25 (3H, s), 4.47 (2H, s), 7.67 (1H, dd, *J* 2.4, 8.7), 7.77 (1H, s), 7.98 (1H, d, *J* 8.7), 8.09 (1H, d, *J* 2.4); ^{13}C-NMR ($CDCl_3$) δ 36.55 (q), 42.09 (t), 124.34 (d), 128.88 (s), 131.19 (d), 131.49 (s), 132.54 (d), 133.34 (d), 134.51 (s), 135.63 (s), 165.42 (s); IR (nujol) 1640 cm^{-1}; MS *m/z* 250 (14, M^++2) 248 (39, M^+), 222 (17), 221 (38), 220 (52), 219 (100),178 (44), 177 (72), 151 (21), 149 (50), 114 (71%); Anal. Calcd. for $C_{11}H_9ClN_4O$; C, 53.13; H, 3.65; N, 22.53. Found: C, 53.20; H, 3.58; N, 22.58.

6c: (43%). M.p. 155-156 °C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 3.25 (3H, s), 4.47 (2H, s), 7.42 (1H, ddd, *J* 2.9, 7.3, 8.9), 7.77 (1H, s), 7.80 (1H, dd, *J* 2.9, 8.9), 8.02 (1H, dd, *J* 4.8, 8.9); ^{13}C-NMR ($CDCl_3$) δ 36.25 (q), 41.70 (t), 118.82 (d), 120.24 (d), 124.73 (d), 125.45 (s), 126.67 (s), 128.23 (s), 130.63 (d), 133.99

(s), 163.79 (s); IR (nujol) 1635 cm^{-1}; MS *m/z* 232 (35, M^+), 204 (44), 203 (100), 161 (55), 133 (94%); Anal. Calcd. for $C_{11}H_9FN_4O$; C, 56.90; H, 3.91; N, 24.13. Found: C, 56.99; H, 4.03; N, 24.27.

6d: (47%). M.p. 197-198 °C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 3.30 (3H, s), 4.54 (2H, s), 7.26 (1H, d, *J* 8.9), 7.83 (1H, s), 8.55 (1H, dd, *J* 2.6, 8.9), 9.00 (1H, d, *J* 2.6); ^{13}C-NMR ($CDCl_3$) δ 36.97 (q), 41.98 (t), 124.28 (d), 127.74 (d), 128.83 (d), 131.70 (d), 134.86 (s), 136.89 (s), 145.76 (s), 147.88 (s), 164.63 (s); IR (nujol) 1650 cm^{-1}; MS *m/z* 259 (51, M^+), 231 (100), 230 (86), 188 (91), 142 (62), 114 (35%); Anal. Calcd. for $C_{11}H_9N_5O_3$; C, 50.97; H, 3.50; N, 27.02. Found: C, 50.88; H, 3.43; N, 27.17.

8-Amino-5-methyl[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one 6e. A mixture of 10% Pd/C (100 mg) and **6d** (103 mg, 0.4 mmol) in MeOH (80 mL) and $CHCl_3$ (80 ml) was stirred under H_2 for 2 h. After filtration through celite, the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica with chloroform/methanol 10:1 as eluent to give **6e** (89 mg, 98%). M.p. 190-192 °C (diisopropyl ether); ^{1}H-NMR ($DMSO_{d6}$) δ 3.06 (3H, s), 4.51 (2H, s), 5.76 (2H, br s, missing after deuteriation), 6.91 (1H, dd, *J* 2.4, 8.7), 7.06 (1H, d, *J* 2.4), 7.54 (1H, d, *J* 8.7), 7.83 (1H, s); IR (nujol) 1630, 3215, 3330 cm^{-1}; MS *m/z* 229 (100, M^+), 201 (47), 200 (69), 174 (20), 158 (43), 130 (30%); Anal. Calcd. for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.53; H, 4.91; N, 30.70.

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References

1. Vida, J.A. in *Medicinal Chemistry*, Wolf, M.W. and Burger, A. Eds; Wiley, New York, 1981, p. 787.
2. Landquist, J.K. in *Comprehensive Heterocylic Chemistry*, Katritzky, A.R. and Rees, C.W. Eds; Pergamon Press, Oxford, 1984, Vol. 1, Ch. 1/06.
3. Sharp, J.T. in *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R. and Rees, C.W. Eds; Pergamon Press, Oxford, 1984, Vol. 7, Ch. 5/18.
4. Hester, J.B., Jr. in *Antianxiety Agents*, Berger, J.G. Ed.; Wiley, New York, 1986, pp. 51-126.
5. Fryer, R.I. in *Comprehensive Medicinal Chemistry*, Hansch, C. Ed; Pergamon Press, New York, 1990, Vol. 3, pp. 539-566.
6. *The Merck Index*, 12th edition, Budavari, S. Ed; Merck & Co., Whitehouse Station, New Jersey, 1996.
7. Fröstl, W.; Maître, L. *Pharmacopsych.* **1989**, *22*, 54.
8. Broggini, G.; Zecchi, G.; Molteni, G. *Gazz. Chim. Ital.* **1997**, *127*, 809.
9. Broggini, G.; Garanti, L.; Molteni, G.; Zecchi, G. *J. Chem. Res.* **1997**, 380 (*S*), 2215 (*M*).
10. Coppola, G.M. *Synthesis* **1980**, 505.
11. Rupe, H.; Kersten, L. *Helv. Chim. Acta*, **1926**, *9*, 578.