Synthesis of Pyrazolo[1,5-*a*]quinoxalines

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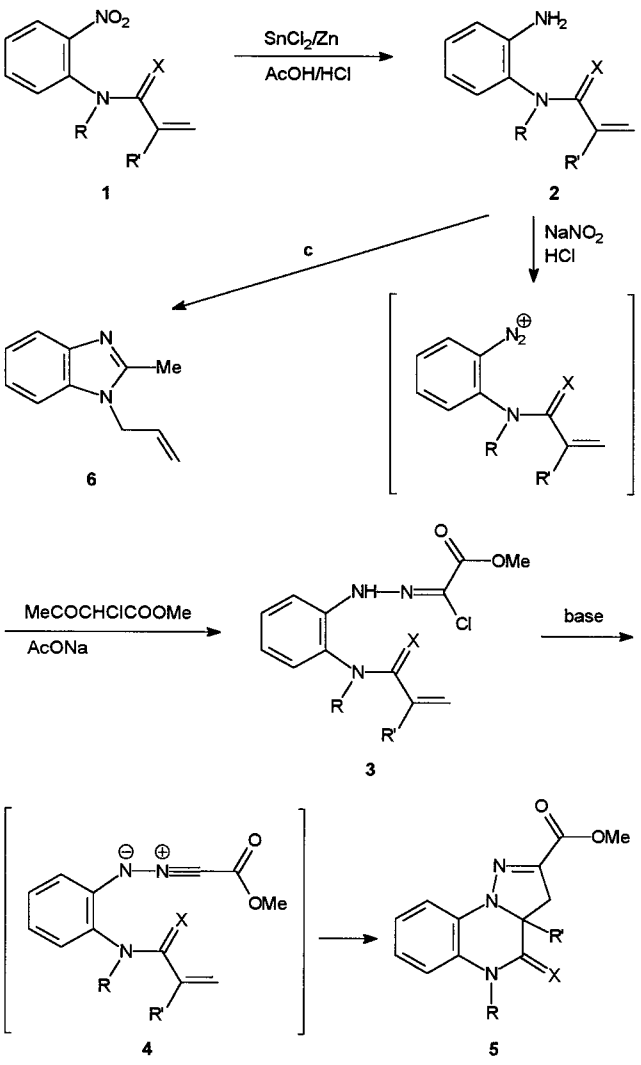
The intramolecular cycloaddition of suitably functionalized nitrilimines provides a general entry to the title compounds.

Despite its structural simplicity and its potential use in pharmacology, the pyrazolo[1,5-*a*]quinoxaline system has been the object of only one occasional report[1] and is still lacking any practical synthetic method. This paper describes a general synthesis of pyrazolo[1,5-*a*]quinoxalines based on the intramolecular nitrilimine cycloaddition principle.[2-4]

The first stage of the synthetic sequence was the preparation of a series of *N,N*-disubstituted 2-nitroanilines **1** having an ethylenic bond in the *N*-substituent (Scheme 1). These nitro derivatives were reduced to the corresponding amino derivatives **2**, which were in turn submitted to diazotization and subsequent coupling with methyl 2-chloroacetoacetate in order to prepare the hydrazonyl chlorides **3** we had thought of as precursors of the appropriate nitrilimines **4**. However, the hydrazonyl chlorides **3** were elusive compounds owing to their pronounced reactivity, even in a weakly basic medium. In fact, the reaction of **2a, b** gave **3a, b** accompanied by some quantity of the corresponding cycloaddition products **5a, b**. On the other hand, compounds **3c, d** were not isolable at all and the cycloaddition products **5c, d** were directly obtained. It was then ascertained that **3a, b** change easily in the presence of triethylamine to give **5a, b** in almost quantitative yield.

The overall yields of the target heterocyclic compounds **5** are very good with entry **c** as the only exception. The modest outcome in the latter case follows from the propensity of **2c** towards the competitive cyclocondensation giving 1-allyl-2-methylbenzimidazole **(6)**.

With the aim of obtaining fully unsaturated pyrazolo[1,5-*a*]quinoxalines, we treated **5a** with a typical dehydrogenating agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[5] Since this attempt failed, we turned our attention towards the possibility of achieving the desired goal by means of intramolecular nitrilimine cycloadditions onto the acetylenic bond. The availability of this route was shown by the exploratory study outlined in Scheme 2, which provided compound **10** in a satisfactory way.



Entry	a	b	c	d
X	H_2	H_2	H_2	O
R	Ph	Ph	Ac	Me
R'	H	Me	H	H

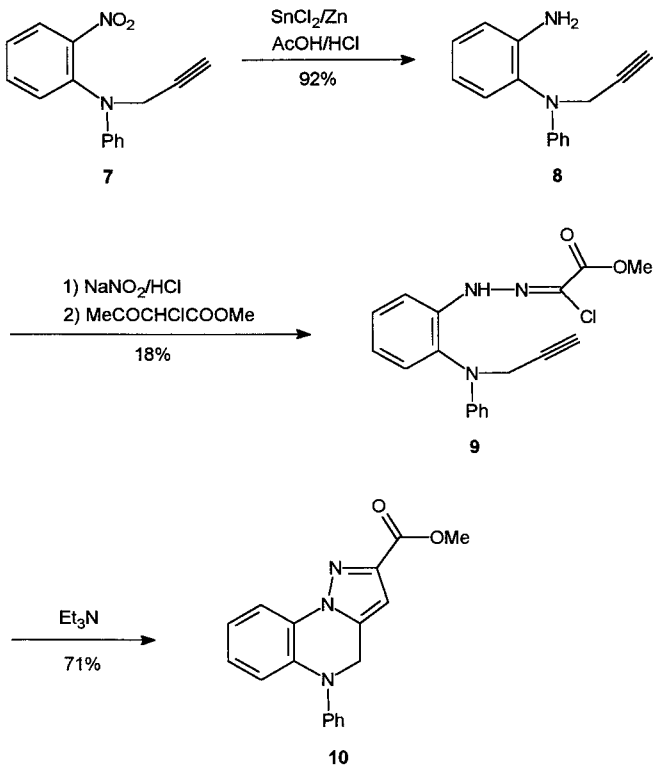
Scheme 1

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 - 70 EQ apparatus. ^{1}H NMR spectra were obtained on a Bruker 300 MHz apparatus; chemical shifts are given as ppm from TMS.

Compounds **1c** and **2c** were prepared according to the literature.[6]

N-(2-Nitrophenyl)-N-(prop-2-enyl)aniline (1a):
A solution of (2-nitrophenyl)aniline (10.0 g, 47.0 mmol) in benzene (200 mL) was treated with 50% aq NaOH (40.0 g, 0.50 mol) and $PhCH_2(Et)_3N^+Br^-$ (1.06 g, 5.0 mmol). Allyl bromide (16.8 g, 0.14 mol) was added and the mixture was refluxed for 12 h. The mixture was washed with H_2O (800 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum (bp 40–60 °C)/EtOAc 5:1 as eluent to give **1a**; yield: 10.8 g (91%); thick oil.

^{1}H NMR ($CDCl_3$): δ = 4.31–4.38 (2 H, m), 5.20 (1 H, dd, J = 10.3, 1.4 Hz), 5.29 (1 H, dd, J = 17.1, 1.4 Hz), 5.97 (1 H, ddt, J = 17.1, 10.3, 5.2 Hz), 6.70–7.82 (9 H, m).
MS (EI): m/z 254 (M^+).



Scheme 2

***N*-(2-Nitrophenyl)-*N*-(2-methylprop-2-enyl)aniline (1b):**
The same procedure described for **1a** was followed using methallyl bromide. Yield: 95%; thick oil.

^{1}H NMR ($CDCl_3$): δ = 1.87 (3H, s), 4.22 (2H, s), 4.92 (1H, s), 5.05 (1H, s), 6.70–7.85 (9H, m).

MS (EI): *m/z* 268 (M^+).

***N*-Methyl-*N*-(2-nitrophenyl)prop-2-enamide (1d):**
A solution of *N*-(2-nitrophenyl)prop-2-enamide[7] (10.0 g, 52.0 mol) in benzene (240 mL) was treated with K_2CO_3 (8.62 g, 62.0 mmol), NaOH (8.12 g, 0.20 mol) and $Bu_4N^+HSO_4^-$ (2.12 g, 6.0 mmol). MeI (10.7 g, 76.0 mmol) was added dropwise at 60°C. The mixture was refluxed for 45 min, then washed with H_2O (800 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum/EtOAc 2:1 to give **1d**; yield: 3.64 g (34%); mp 56°C (from hexane/benzene).

IR (Nujol): ν = 1670 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.29 (3H, s), 5.40–6.00 (2H, m), 6.38 (1H, dd, *J* = 16.4, 2.3 Hz), 7.20–8.10 (4H, m).

MS (EI): *m/z* 206 (M^+).

***N*-(2-Aminophenyl)anilines 2a, b, d; General Procedure:**
A solution of **1** (4.2 mmol) in glacial AcOH (21 mL) and 37% aq HCl (2.7 mL) was treated with $SnCl_2 \cdot 2H_2O$ (2.30 g, 10.2 mmol) and powdered Zn (0.67 g, 10.2 mmol). The mixture was stirred at r.t. for 4.5 h and then basified with 30% aq NaOH. The organic layer was extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated under reduced pressure yielding **2** (see Table 1).

Hydrazonyl Chlorides 3; General Procedure:
$NaNO_2$ (1.00 g, 14.5 mmol) was added portionwise to a solution of **2** (9.9 mmol) in 12 M aq HCl (4 mL) and MeOH (10 mL) under vigorous stirring and cooling at 0°C. After 15 min, the pH of the cold mixture was adjusted to 5 with NaOAc and then methyl 2-chloroacetoacetate (1.48 g, 9.9 mmol) was added whilst it was cooled and stirred. The mixture was stirred at r.t. for 2.5 h and extracted with Et_2O. The organic layer was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column. Eluents and products are described in Tables 1 and 2. In the case of **2c**, a further product was 1-allyl-2-methylbenzimidazole (**6**); yield: (58%); mp 42°C (from *i*-Pr_2O).

^{1}H NMR ($CDCl_3$): δ = 2.46 (3H, s), 4.50 (2H, d, *J* = 4.5 Hz), 4.75 (1H, d, *J* = 17.5 Hz), 5.06 (1H, d, *J* = 10.5 Hz), 5.55–6.00 (1H, m), 6.90–7.75 (4H, m).

MS (EI): *m/z* 172 (M^+).

Pyrazolo[1,5-*a*]quinoxalines 5a, b; General Procedure:
A solution of **3** (5.0 mmol) in anhyd benzene (165 mL) was treated with Et_3N (1.01 g, 10.0 mmol) and the mixture was refluxed under stirring for 12 h. The solvent was removed under reduced pressure to give cycloadduct **5a, b** (Table 2).

***N*-(2-Nitrophenyl)-*N*-(propynyl)aniline (7):**
The same procedure described for **1a** was followed using propargyl bromide. Yield: 74%; mp 83°C (from *i*-Pr_2O).

^{1}H NMR ($CDCl_3$): δ = 2.29 (1H, t, *J* = 2.5 Hz), 4.42 (1H, d, *J* = 2.5 Hz), 6.65–7.95 (9H, m).

MS (EI): *m/z* 252 (M^+).

***N*-(2-Aminophenyl)-*N*-(propynyl)aniline (8):**
The same procedure used for aminoanilines **2** was followed. Yield: 92%; thick oil.

Table 1. Preparation of Intermediates **2** and **3**

Compound[a]	Yield (%)	Mp (°C)	IR (Nujol) ν (cm^{-1})	MS (70 eV) *m/z* (M^+)	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)
2a	77	Oil[b]	3470, 3370, 3290	224	3.75 (2H, br s), 4.23 (2H, d, *J* = 5.4), 5.20 (2H, d, *J* = 10.3), 5.29 (1H, d, *J* = 17.2), 5.92–6.08 (1H, m), 6.60–7.35 (9H, m)
2b	89	Oil[b]	3470, 3370, 3280	238	1.80 (3H, s), 3.72 (2H, br s), 4.11 (2H, s), 4.90 (1H, s), 5.05 (1H, s), 6.50–7.30 (9H, m)
2d	31	Oil[b]	3440, 3350, 3230, 1690	176	1.73 (2H, br s), 3.78 (3H, s), 5.75 (1H, dd, *J* = 11.2, 1.4), 6.54 (1H, dd, *J* = 17.2, 1.4), 6.83 (1H, dd, *J* = 17.2, 11.2), 7.10–7.90 (4H, m)
3a	35[c,d]	48[e]	3310, 1730	343	3.90 (3H, s), 4.23 (2H, d, *J* = 5.3), 5.09–5.45 (2H, m), 5.75–6.27 (1H, m), 6.60–7.80 (9H, m), 8.80 (1H, br s)
3b	3[c,f]	45[e]	3310, 1730	357	1.77 (3H, s), 3.89 (3H, s), 4.13 (2H, s), 4.94 (1H, s), 5.02 (1H, s), 6.60–7.70 (9H, m), 8.75 (1H, br s)

[a] Isolation of **3c, d** was precluded by their pronounced reactivity (see text).
[b] Samples of analytical purity were not available.
[c] In addition to the corresponding cycloadducts **5a** (17%) and **5b** (25%).
[d] Eluent for chromatography: CH_2Cl_2.
[e] Satisfactory microanalyses were obtained (C ± 0.15, H ± 0.12, N ± 0.16).
[f] Eluent for chromatography: LP/EtOAc (1.5 : 1).

Table 2. Preparation of Pyrazolo[1,5-*a*]quinoxalines **5**

Compound[a]	Eluent	Yield (%)	mp (°C)	IR (Nujol) ν (cm^{-1})	MS (70 eV) m/z (M^+)	^1H NMR ($CDCl_3$) δ, J (Hz)
5a	–	91[b]	141	1720	307	2.96 (1 H, dd, J = 17.8, 7.3), 3.27 (2 H, overlapping), 3.72 (1 H, dd, J = 11.9, 3.4), 3.87 (3 H, s), 4.20–4.31 (1 H, m), 6.75–7.65 (9 H, m)
5b	–	14[b]	136	1720	321	1.35 (3 H, s), 3.03 (2 H, s), 3.35 (1 H, d, J = 12.5), 3.57 (1 H, d, J = 12.5), 3.84 (3 H, s), 6.70–7.60 (9 H, m)
5c	EtOAc/MeOH (9 : 1)	9[c]	130	1730, 1690	273	2.65 (3 H, s), 2.98 (1 H, dd, J = 16.5, 9.0), 3.35 (1 H, dd, J = 16.5, 6.1), 3.87 (3 H, s), 4.24–4.37 (2 H, m), 4.60–5.35 (1 H, m), 7.15–7.85 (4 H, m)
5d	CH_2Cl_2/Et_2O (5 : 1)	36[c]	129	1730, 1690	259	3.63 (1 H, dd, J = 17.8, 11.5), 3.92 (6 H, s), 4.48 (1 H, dd, J = 17.8, 8.0), 6.06 (1 H, dd, J = 11.5, 8.0), 7.26–7.76 (4 H, m)

[a] All compounds gave satisfactory microanalyses (C ± 0.16, H ± 0.17, N ± 0.14).
[b] Starting from **3**.
[c] Starting from **2**.

IR (Nujol): ν = 3470, 3370, 3290, 2210 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.29 (1 H, t, J = 2.5 Hz), 3.85 (2 H, br s), 4.30 (1 H, d, J = 2.5 Hz), 6.65–7.65 (9 H, m), 9.80 (1 H, br s).

MS (EI): m/z 222 (M^+).

Hydrazonyl Chloride 9:

$NaNO_2$ (362 mg, 5.2 mmol) was added portionwise to a solution of **7** (780 mg, 3.5 mmol) in 12 M aq HCl (2 mL) and H_2O (2 mL) under vigorous stirring and cooling at 0 °C. After 15 min the pH of the cold mixture was adjusted to 5 with NaOAc and then methyl 2-chloroacetoacetate (527 mg, 3.5 mmol) was added whilst it was cooled and stirred. The mixture was stirred at r.t. for 3 h and extracted with Et_2O. The organic layer was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column with CH_2Cl_2 giving **9**; yield: 214 mg (18%); mp 108 °C (from *i*-Pr_2O).

IR (Nujol): ν = 3300, 3270, 1725 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.29 (1 H, t, J = 2.5 Hz), 3.90 (3 H, s), 4.30 (2 H, d, J = 2.5 Hz), 6.67–7.30 (9 H, m), 9.80 (1 H, br s).

MS (EI): m/z 341 (M^+).

Pyrazolo[1,5-*a*]quinoxaline (10):

A solution of **9** (682 mg, 2.0 mmol) in anhyd benzene (85 mL) was treated with Et_3N (0.40 g, 4.0 mmol) and the mixture was refluxed under stirring for 10 h. The solvent was removed under reduced pressure to give cycloadduct **10**; yield: 416 mg (71%); mp 122 °C (from *i*-Pr_2O).

IR (Nujol): ν = 1730 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.96 (3 H, s), 4.87 (2 H, s), 6.70 (1 H, s), 6.89–8.06 (9 H, m).

MS (EI): m/z 305 (M^+).

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(1) Albini, A.; Bettinetti, G.; Minoli, G. *J. Am. Chem. Soc.* **1991**, *113*, 6298.
(2) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley – Interscience: New York, 1984; Vol. II, Chapter 12.
(3) Padwa, A.; Schoffstall, A.M. In *Advances in Cycloaddition*; Curran, D.P., Ed.; JAI: London, 1990; pp 1–89.
(4) Broggini, G.; Bruché, L.; Garanti, L.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 433.
(5) Theobald, R.S. In *Rodd's Chemistry of Carbon Compounds*; Ansell, M.F., Ed.; Elsevier: Amsterdam, 1986; Vol. IV/C.
(6) Beckwith, A.L.J.; Meijs, G.F. *J. Org. Chem.* **1987**, *52*, 1922.
(7) Catto, A.; Motta, G.; Tajana, A.; Cazzulani, P.; Nardi, D.; Leonardi, A. *J. Med. Chem.* **1987**, *30*, 13.