

SYNTHESIS OF THE NEW PYRAZOLO[4,3-*c*]PYRROLIZINE SKELETON VIA INTRAMOLECULAR NITRILIMINE CYCLOADDITION

Giorgio Molteni*

Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale,
via Golgi 19, 20133 Milano, Italy

Abstract – Starting from the appropriate 1-substituted pyrrol-2-yl- (**1**) or indol-2-ylcarboxylic acid (**6**), the hydrazonyl chlorides (**3**) or (**8**) have been synthesised respectively. Their base treatment promoted the *in situ* generation of the corresponding nitrilimines (**4**) or (**9**), whose intramolecular 1,3-dipolar cycloaddition gave the title compounds in nearly quantitative yields.

INTRODUCTION

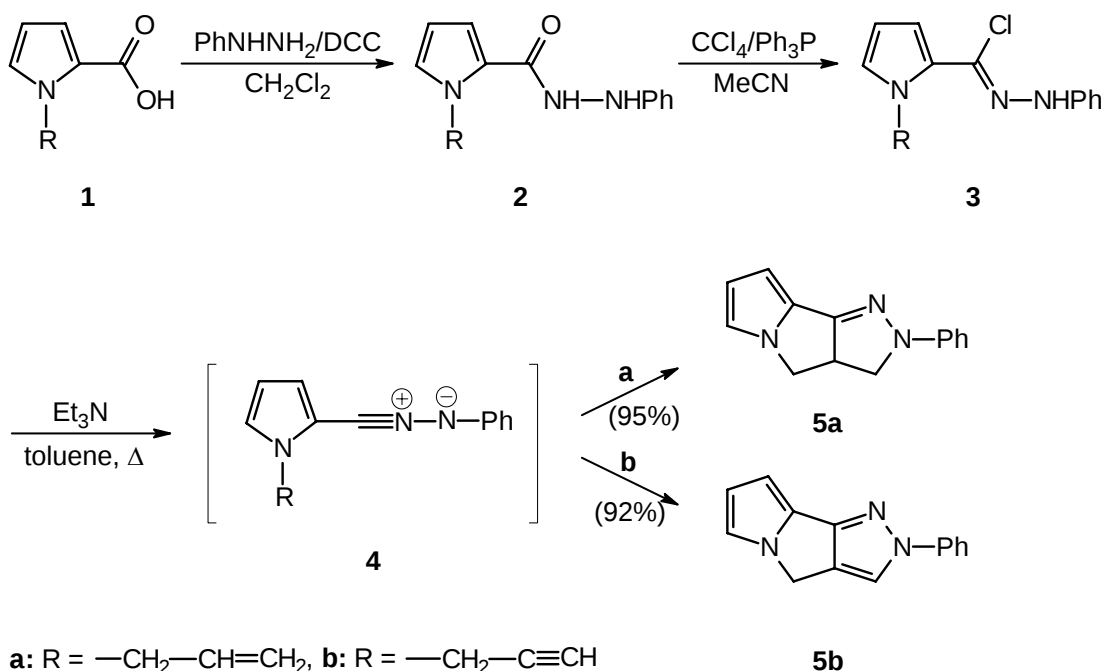
Intramolecular reactions of nitrilimines represents a fruitful source of heterocycles.¹ In particular, the intramolecular 1,3-dipolar cycloadditions of suitably functionalized nitrilimines give rise to a huge variety of fused or bridged bi- or tricyclic heterocycles bearing the pyrazole ring.^{1,2} A number of literature examples are available in which the nitrilimine and the dipolarophilic functionalities are joined by an alkyl chain³ or by a benzene ring,⁴ but there is a paucity of data concerning the use of small heterocyclic units as suitable linkers between the interacting functionalities. In this note it is presented the first case of intramolecular nitrilimine cycloaddition onto the ethylenic and the acetylenic bond, in which the 1,3-dipolar and the dipolarophilic fragments are joined by the pyrrole or the indole ring.

RESULTS AND DISCUSSION

In order to obtain the acyl hydrazides (**2**), 1-allyl-2-hydroxycarbonylpyrrole (**1a**)⁵ or 1-propargyl-2-hydroxycarbonylpyrrole (**1b**) were treated with phenylhydrazine and dicyclohexylcarbodiimide as condensating agent (Scheme 1). Hydrazonyl chlorides (**3**) were synthesised from corresponding **2** using chlorinating agent, triphenylphosphine-carbon tetrachloride according to the Wolkoff's method.⁶ The labile nitrilimine intermediates (**4**) were generated *in situ* by refluxing the dry toluene solution of **3** in the presence of a large excess (5 eq.) of triethylamine, according to the classic Huisgen's nitrilimine

cycloaddition protocol.⁷ Their intramolecular cycloadditions proceeded smoothly giving the pyrazolo[4,3-*c*]pyrrolizine cycloadducts (**5a,b**) in nearly quantitative yields (Scheme 1). The latter structures rely unambiguously upon analytical and spectral data. In particular, the ¹H-NMR spectrum of cycloadduct (**5a**) shows the set of four double of doublets at δ 3.14-4.46 due to the non-aromatic hydrogens, which are typical for such proton arrangement.³ On the other hand, ¹H-NMR spectrum of **5b** shows a sharp singlet at δ 7.75 which is in full agreement with proton resonance of 5- unsubstituted pyrazoles.⁸

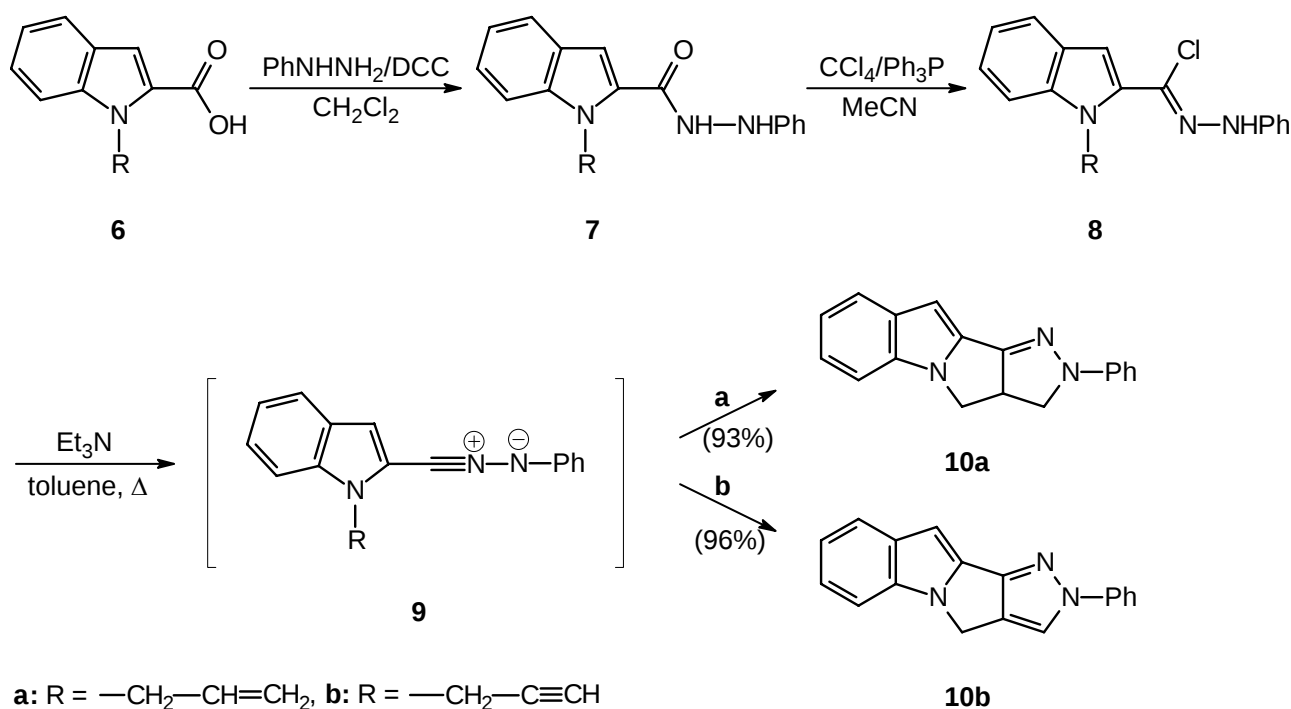
Scheme 1



The same synthetic and spectroscopic arguments also applies to cycloadducts (**10a**) and (**10b**) which were obtained starting from 1-allyl-2-hydroxycarbonylindole (**6a**)⁹ or 1-propargyl-2-hydroxycarbonylindole (**6b**),¹⁰ respectively (Scheme 2).

Intramolecular cycloaddition of nitrilimines (**4**) and (**9**) led to products (**5**) and (**10**) in which the pyrazole ring is substituted in the 4-position. This regioselectivity is opposite to that expected from the intermolecular process upon monosubstituted ethylenes or acetylenes, which usually operates under the HOMO-dipole (LUMO-dipolarophile) control.¹¹

Scheme 2



EXPERIMENTAL

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. MS spectra were determined with a VG-70EQ apparatus. $^1\text{H-NMR}$ (300 MHz) spectra were taken with a Bruker AMX 300 instrument (in CDCl_3 solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and J values are given in Hz.

1-Propargyl-2-hydroxycarbonylpyrrole (1b). A solution of 2-ethoxycarbonylpyrrole (1.76 g, 13.0 mmol) and propargyl bromide (1.79 g, 15.0 mmol) in dry toluene (35 mL) was treated with triethylamine (1.52 g, 15.0 mmol) and refluxed for 6 h. The undissolved material was filtered off, the solvent was evaporated under reduced pressure, and the residue was dissolved in tetrahydrofuran (25 mL). Aqueous 2M sodium hydroxide (25 mL) was added and the mixture was heated to 50°C for 5 h. The pH was adjusted to 1 with aqueous 4M hydrochloric acid and the mixture was extracted twice with ethyl acetate (2 x 100 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure to give **1b** (1.55 g, 80%) as white amorphous powder. mp 140°C (from ethanol); IR (nujol): 3360, 2120 (cm^{-1}); $^1\text{H-NMR}$: 2.48 (1H, t, $J=2.5$ Hz), 5.14 (2H, d, $J=2.5$ Hz), 6.17 (1H, dd, $J=3.9, 2.7$ Hz), 7.08 (1H,

dd, $J=3.9, 1.6$ Hz), 7.17 (1H, dd, $J=2.7, 1.6$ Hz), 10.40 (1 H, br s); MS: 149 m/z (M^+). *Anal.* Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.46; H, 4.70; N, 9.44.

Synthesis of acyl hydrazides (2) and (7). A solution of the appropriate 1-substituted pyrrol-2-yl- (1) or indol-2-ylcarboxylic acid (6) (5.5 mmol) in dry dichloromethane (55 mL) was treated with dicyclohexylcarbodiimide (1M solution in dichloromethane, 6.0 mL) and stirred at rt for 30 min. Phenylhydrazine (0.81 g, 7.5 mmol) was added and the mixture was stirred at rt for 12 h. The reaction mixture was poured onto crushed ice (60 mL), the organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure. The dark red residue was chromatographed on a silica gel column with ethyl acetate-hexane (3:1) giving acylhydrazides (2) or (7).

Compound (2a) (41%) as white amorphous powder. mp 67°C (from diisopropyl ether); IR (nujol): 3250, 1640 (cm^{-1}); 1H -NMR: 4.94 (2H, dt, $J=5.4, 2.8$ Hz), 5.07 (1H, dd, $J=3.0, 1.5$ Hz), 5.13 (1H, dd, $J=11.5, 1.4$ Hz), 5.90-6.10 (1H, m), 6.20 (1H, br d, $J=3.5$ Hz), 6.18 (1H, dd, $J=4.0, 2.7$ Hz), 6.78 (1H, dd, $J=4.0, 1.7$ Hz), 6.90-7.20 (6H, m), 7.60 (1H, br s); MS: 241 m/z (M^+). *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.62; H, 6.31; N, 17.48.

Compound (2b) (46%) as white amorphous powder. mp 73°C (from diisopropyl ether-methanol); IR (nujol): 3260, 2130, 1650 (cm^{-1}); 1H -NMR: 2.40 (1H, t, $J=2.5$ Hz), 5.20 (2H, d, $J=2.5$ Hz), 6.15 (1H, br d, $J=3.8$ Hz), 6.20 (1H, dd, $J=4.0, 2.7$ Hz), 6.77 (1H, dd, $J=4.0, 1.6$ Hz), 6.90-7.20 (6H, m), 7.70 (1H, br s); MS: 239 m/z (M^+). *Anal.* Calcd for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.32; H, 5.52; N, 17.63.

Compound (7a) (52%) as pale yellow amorphous solid. mp 61°C (from diisopropyl ether); IR (nujol): 3270, 1650 (cm^{-1}); 1H -NMR: 4.90 (2H, dt, $J=17.4, 1.1$ Hz), 5.08 (1H, dd, $J=10.3, 1.0$ Hz), 5.13 (1H, d, $J=5.1$ Hz), 5.90-6.00 (1H, m), 6.30 (1H, br d, $J=3.5$ Hz), 6.90-7.60 (10H, m), 8.20 (1H, br s); MS: 291 m/z (M^+). *Anal.* Calcd for $C_{18}H_{17}N_3O$: C, 74.21; H, 5.88; N, 14.42. Found: C, 74.17; H, 5.91; N, 14.49.

Compound (7b) (50%) as pale yellow amorphous solid. mp 68°C (from diisopropyl ether-methanol); IR (nujol): 3270, 2130, 1640 (cm^{-1}); 1H -NMR: 2.26 (1H, t, $J=2.4$ Hz), 5.42 (2H, d, $J=2.4$ Hz), 6.28 (1H, br d, $J=4.7$ Hz), 7.12 (1H, s), 6.90-7.80 (9H, m), 7.90 (1H, br s); MS: 289 m/z (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.68; H, 5.25; N, 14.57.

Synthesis of hydrazoneoyl chlorides (3) and (8). A solution of the appropriate acylhydrazide (2) or (7) (4.0 mmol) in dry acetonitrile (40 mL) and carbon tetrachloride (3.08 g, 20.0 mmol) was treated with triphenylphosphine (5.11 g, 65 mmol) and stirred at rt for 12 h. Brine (25 mL) was added to reaction mixture, the organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure. The dark red residue was chromatographed on a silica gel column with ethyl acetate-hexane (2:1) giving hydrazoneoyl chlorides (3) or (8).

Compound (**3a**) (59%) as yellow amorphous powder. mp 71°C (from diisopropyl ether-isopropanol); IR (nujol): 3280 (cm⁻¹); ¹H-NMR: 4.90-5.10 (3H, m), 5.19 (1H, dd, *J*=10.4, 1.4 Hz), 6.00-6.15 (1H, m), 6.20 (1H, dd, *J*=3.9, 2.7 Hz), 6.57 (1H, dd, *J*=3.9, 1.9 Hz), 6.79 (1H, dd, *J*=2.7, 0.8 Hz), 6.90-7.30 (5H, m), 7.90 (1H, br s); MS: 259 *m/z* (M⁺). *Anal.* Calcd for C₁₄H₁₄N₃Cl: C, 64.74; H, 5.43; N, 13.65. Found: C, 64.71; H, 5.45; N, 13.70.

Compound (**3b**) (56%) as yellow amorphous powder. mp 63°C (from diisopropyl ether-methanol); IR (nujol): 3280, 2130 (cm⁻¹); ¹H-NMR: 2.42 (1H, t, *J*=2.5 Hz), 5.17 (2H, d, *J*=2.5 Hz), 6.20 (1H, dd, *J*=3.9, 2.6 Hz), 6.70 (1H, dd, *J*=3.9, 1.8 Hz), 6.95 (1H, dd, *J*=2.6, 0.7 Hz), 6.90-7.30 (5H, m), 7.86 (1H, br s); MS: 257 *m/z* (M⁺). *Anal.* Calcd for C₁₄H₁₂N₃Cl: C, 65.25; H, 4.69; N, 13.76. Found: C, 65.29; H, 4.72; N, 13.81.

Compound (**8a**) (57%) as pale yellow amorphous powder. mp 102°C (from diisopropyl ether); IR (nujol): 3220 (cm⁻¹); ¹H-NMR: 4.93 (1H, dd, *J*=17.3, 1.2 Hz), 5.16 (1H, dd, *J*=10.3, 1.1 Hz), 5.25-5.28 (2H, m), 6.00-6.15 (1H, m), 6.90-7.60 (10H, m), 8.10 (1H, br s); MS: 309 *m/z* (M⁺). *Anal.* Calcd for C₁₈H₁₆N₃Cl: C, 69.79; H, 5.21; N, 13.56. Found: C, 69.83; H, 5.18; N, 13.61.

Compound (**8b**) (59%) as yellow amorphous powder. mp 109°C (from diisopropyl ether); IR (nujol): 3220, 2120 (cm⁻¹); ¹H-NMR: 2.32 (1H, t, *J*=2.5 Hz), 5.40 (2H, d, *J*=2.5 Hz), 7.04 (1H, s), 6.90-7.70 (9H, m), 8.12 (1H, br s); MS: 307 *m/z* (M⁺). *Anal.* Calcd for C₁₈H₁₄N₃Cl: C, 70.24; H, 4.59; N, 13.65. Found: C, 70.28; H, 4.63; N, 13.69.

Intramolecular cycloadditions of hydrazoneoyl chlorides (3) and (8). A solution of the appropriate hydrazoneoyl chloride (**3**) or (**8**) (2.5 mmol) in dry toluene (125 mL) was treated with triethylamine (1.01 g, 10.0 mmol) and refluxed for 5 h. The reaction mixture was evaporated under reduced pressure, and then the residue was crystallised from diisopropyl ether giving pure cycloadducts (**5**) or (**10**).

Compound (**5a**) (95%) as white amorphous powder. mp 144°C; ¹H-NMR: 3.14 (1H, dd, *J*=14.2, 8.7 Hz), 3.80 (1H, dd, *J*=10.0, 7.8 Hz), 4.05-4.15 (1H, m), 4.28 (1H, dd, *J*=10.0, 2.1 Hz), 4.46 (1H, dd, *J*=14.2, 1.9 Hz), 6.42 (1H, dd, *J*=3.9, 2.8 Hz), 6.54 (1H, dd, *J*=4.0, 1.5 Hz), 6.90-7.30 (6H, m); MS: 223 *m/z* (M⁺). *Anal.* Calcd for C₁₄H₁₃N₃: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.27; H, 5.90; N, 18.88.

Compound (**5b**) (92%) as white amorphous powder. mp 164°C; ¹H-NMR: 4.90 (2H, s), 6.28 (1H, dd, *J*=2.8, 1.4 Hz), 6.43 (1H, dd, *J*=3.7, 2.8 Hz), 6.97 (1H, dd, *J*=3.7, 1.4 Hz), 7.20-7.40 (5H, m), 7.75 (1H, s); MS: 221 *m/z* (M⁺). *Anal.* Calcd for C₁₄H₁₁N₃: C, 76.00; H, 5.01; N, 18.99. Found: C, 75.96; H, 4.98; N, 19.06.

Compound (**10a**) (93%) as white amorphous powder. mp 205°C; ¹H-NMR: 3.22 (1H, dd, *J*=13.7, 8.3 Hz), 3.83 (1H, dd, *J*=9.3, 7.2 Hz), 4.10-4.25 (1H, m), 4.38 (1H, dd, *J*=13.7, 1.4 Hz), 4.67 (1H, dd, *J*=9.3, 1.3 Hz), 6.82 (1H, s), 6.90-7.70 (9H, m); MS: 273 *m/z* (M⁺). *Anal.* Calcd for C₁₈H₁₅N₃: C, 79.09; H, 5.53; N, 15.37. Found: C, 79.13; H, 5.56; N, 15.42.

Compound (**10b**) (96%) as white amorphous powder. mp 215°C; ¹H-NMR: 5.02 (2H, s), 6.77 (1H, s), 7.10-7.70 (9H, m), 7.85 (1H, s); MS: 271 *m/z* (M⁺). *Anal.* Calcd for C₁₈H₁₃N₃: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.72; H, 4.80; N, 15.56.

ACKNOWLEDGEMENTS

Thanks are due to MURST and CNR for financial support.

REFERENCES

1. G. Broggini, G. Molteni, and G. Zecchi, *Heterocycles*, 1998, **47**, 541.
2. J. T. Sharp, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', ed. by A. Padwa and W. H. Pearson, Wiley, New York, 2002, pp. 473-538.
3. G. Broggini, G. Molteni, T. Pilati, and G. Zecchi, *Synth. Commun.*, 2001, **31**, 3799.
4. G. Broggini, L. Garanti, G. Molteni, and T. Pilati, *Synth. Commun.*, 2001, **31**, 2649.
5. K. Maruta, R. Nagata, K. Iwai, K. Ushiroda, and K. Yoshida, Patent WO 2003-JP3935 20030328 (*Chem. Abstr.*, 2003, **139**, 365221).
6. P. Wolkoff, *Can. J. Chem.*, 1975, **53**, 1333.
7. R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.
8. A. R. Katritzky and J. M. Lagowski, 'Comprehensive Heterocyclic Chemistry,' ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 5, pp. 1-38.
9. A. Padwa, D. L. Hertzog, W. R. Nadler, M. H. Osterhout, and A. T. Price, *J. Org. Chem.*, 1994, **59**, 1418.
10. E. Defossa, U. Heinelt, O. Klingler, G. Zoller, F. Al-Obeidi, A. Walser, P. Wildgoose, and H. Matter, Patent WO 9933800 A1 19990708 (*Chem. Abstr.*, 1999, **131**, 87814).
11. (a) K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287; (b) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301; (c) P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, 1976, **98**, 6397.
12. G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95.