STUDIES ON ISONITRILES AND RELATED COMPOUNDS. SYNTHESIS OF 1*H*-PYRROLE AND 1*H*-IMIDAZOLE DERIVATIVES VIA 1,3-DIPOLAR CYCLOADDITION

Ricardo Bossio,[a] Stefano Marcaccini,[a*] Paola Paoli,[b] Roberto Pepino,[a] and Cecilia Polo[c]

[a] *CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Dipartimento di Chimica Organica " Ugo Schiff ", Universita' di Firenze, via G. Capponi 9, 50121 Firenze, Italy*

[b] *Dipartimento di Energetica, Universita' di Firenze, via S.Marta 3, 50139, Firenze, Italy*

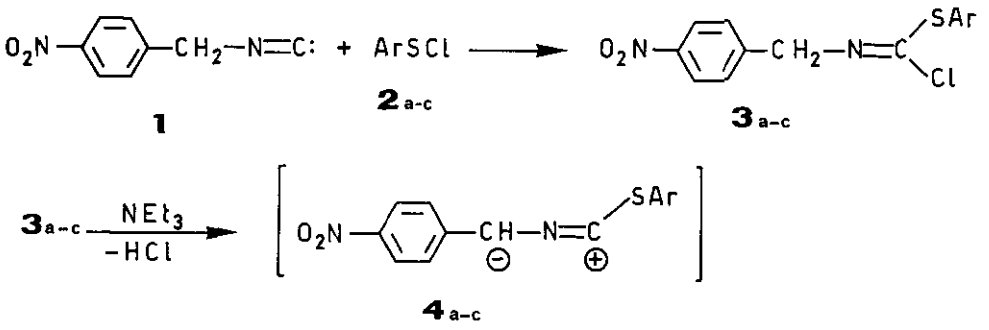
[c] *Facultad de Veterinaria, Universidad de Extremadura, 10071 Cáceres, Spain*

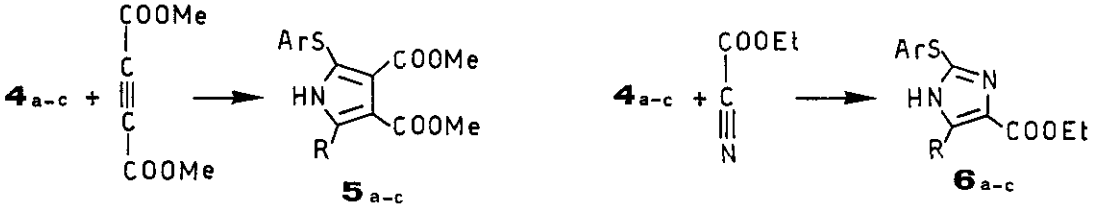
Abstract — 4-Nitrobenzyl isocyanide (**1**) reacted with arylsulfenyl chlorides (**2**) to give isothiocarbamoyl chlorides (**3**). Treatment of **3** with NEt_3 afforded nitrile ylides (**4**) which reacted with stoichiometric amounts of dimethyl acetylenedicarboxylate to give 1*H*-pyrroles (**5**) and with an excess of the same reagent to give dimethyl 2-substituted maleates (**7**). The reaction of **4** with ethyl cyanoformate afforded 1*H*-imidazoles (**6**).

In a previous paper[1] we described the synthesis of some 2*H*-pyrrole and 4*H*-imidazole derivatives by means of 1,3-dipolar cycloaddition of new nitrile ylides. These nitrile ylides were generated *in situ* by treating *N*-(1-cyanoethyl)-*S*-arylisothiocarbamoyl chlorides with NEt_3.

Since isothiocarbamoyl chlorides can be easily prepared by reacting sulfenyl chlorides with isonitriles,[2] the choice of the isonitrile is the only problem in the synthesis of suitable precursors of nitrile ylides.

This paper deals with the synthesis of new 1*H*-pyrrole and 1*H*-imidazole derivatives starting from 4-nitrobenzyl isocyanide (**1**). The first step consisted of the reaction between **1** and arylsulfenyl chlorides (**2**) which afforded *N*-(4-nitrobenzyl)-*S*-arylisothiocarbamoyl chlorides (**3**). Upon treatment of a solution of **3** with NEt_3, a solution containing the 1,3-dipolar species (**4**) was obtained. When the 1,3-dipole was generated in the presence of dimethyl acetylenedicarboxylate or ethyl cyanoformate, 1,3-dipolar cycloaddition took place affording 1*H*-pyrroles (**5**) or 1*H*-imidazoles (**6**), respectively.





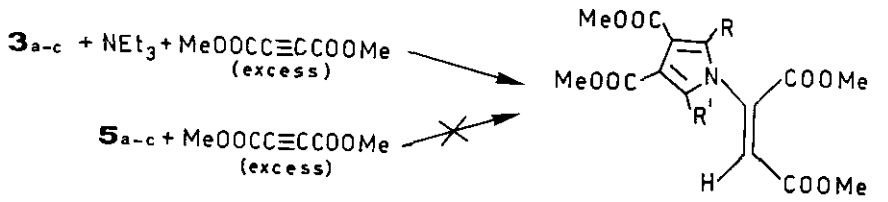
a R = 4-nitrophenyl Ar = 2-nitrophenyl

b R = 4-nitrophenyl Ar = 2-nitro-4-chlorophenyl

c R = 4-nitrophenyl Ar = 4-chlorophenyl

On the present synthesis some remarks are to be made. We obtained **1** in 65 % yield by dehydrating *N*-(4-nitrobenzyl)formamide with $POCl_3/NEt_3$. Although **1** was obtained in lower yield than the literature procedure,[3] this method has the advantage that $POCl_3$ is used in place of the highly toxic phosgene. An attempt to perform the dehydration with PPh_3/CCl_4 failed. The reaction between arylsulfenyl chlorides (**2**) and **1** occurred very easily, even in very mild conditions, to give isothiocarbamoyl chlorides (**3**) in nearly quantitative yields. Dipolar cycloaddition of nitrile ylides (**4**) with dimethyl acetylenedicarboxylate occurred in fair yields at room temperature whereas with the less reactive ethyl cyanoformate the reaction was performed at 60 °C in the presence of a strong excess of the dipolarophile.

When a large excess of dimethyl acetylenedicarboxylate was employed we noted an unexpected and interesting reaction in which two molecules of dimethyl acetylenedicarboxylate took part to give a series of derivatives of maleic acid. It must be noted that the formation of compounds (**7**) does not occur via the intermediacy of pyrrole derivatives (**5**). In fact, on prolonging heating of **5** with an excess of dimethyl acetylenedicarboxylate no reaction took place, even in the presence of NEt_3.

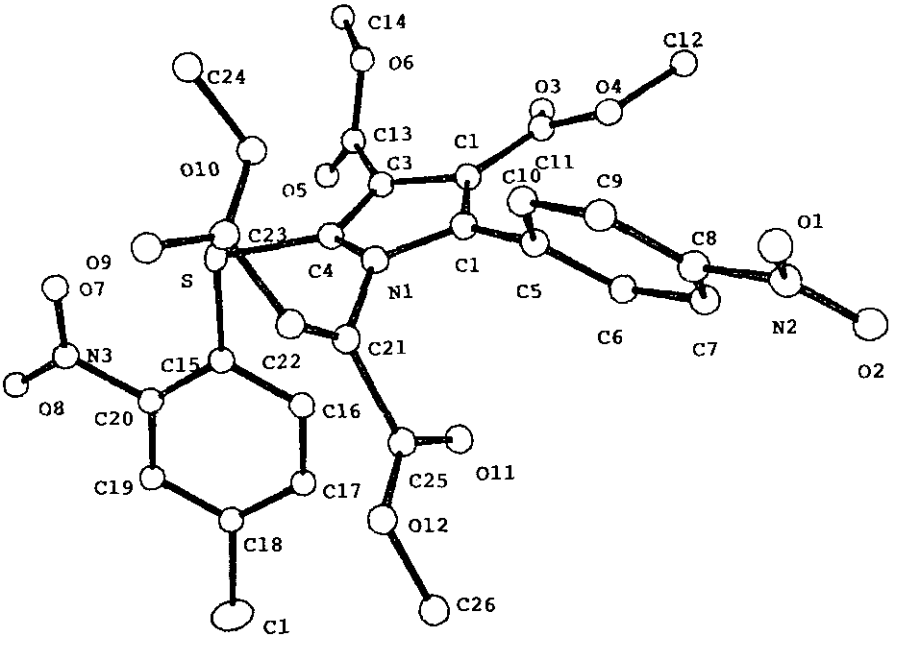


7a-c

a R = 4-nitrophenyl R' = 2-nitrophenylthio
b R = 4-nitrophenyl R' = 2-nitro-4-chlorophenylthio
c R = 4-nitrophenyl R' = 4-chlorophenylthio

The structure of compounds (7) was assigned on the basis of their ^{1}H-nmr spectra. In these spectra, that are closely similar, no exchangeable proton was detected and this agrees with the presence of a pyrrole ring with a substituent in 1 position. Furthermore the presence of four Me singlets agrees with the presence of four ester groups. A further confirmation of the structure of compounds (7) was obtained by performing the X-ray analysis of 7b.

Figure: Diagram showing the structure of 7b



EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ^{1}H-nmr spectra were recorded with a Perkin-Elmer R32 and a Varian Gemini 200 instruments. Chemical shifts are reported in ppm (δ) from TMS. The ir spectra were measured on a Perkin-Elmer 881 apparatus.

4-Nitrobenzyl Isocyanide (1)

A solution of $POCl_3$ (10.22 g, 66.6 mmol) in CH_2Cl_2 (10 ml) was slowly added to a well-stirred suspension of *N*-(4-nitrobenzyl)formamide (10 g, 55.5 mmol) and NEt_3 (22.4 g, 221.4 mmol) in CH_2Cl_2 (70 ml) maintaining the temperature at -20 °C. The resulting mixture was allowed to stand until the temperature rose to 10 °C and then stirred with a solution of Na_2CO_3 (18.33 g, 172 mmol) in 150 ml of water. The resulting suspension was filtered, the filtrate was transferred in a separatory funnel and the phases were separated. The organic layer was washed with two 100 ml portions of water, dried over $MgSO_4$ and then evaporated to dryness. The residue was dissolved in 200 ml of hot ethanol, decolourized with charcoal and then evaporated to dryness. The residue was recrystallized from isopropyl ether to give 5.87 g (65 %) of **1**. mp 106-107 °C (reported,[3] mp 103-104 °C); ^{1}H-nmr (DMSO-d_6): 5.13 (s, 2H, CH_2); ir (KBr): 2161 cm^{-1}. *Anal.* Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.08; H, 3.78; N, 17.02.

Arylsulfenyl Chlorides (2a-c)

Compounds **2a**[4], **2b**[5], and **2c**[6] were prepared according to the known methods.

N-(4-Nitrobenzyl)-*S*-arylisothiocarbamoyl Chlorides (3a-c)

General Procedure- The calculated amount (12.3 mmol) of the appropriate sulfenyl chloride (**2**) in CH_2Cl_2 (15 ml) was slowly dropped into a well-stirred solution of **1** (2 g, 12.3 mmol) in CH_2Cl_2 (50 ml), maintaining the temperature at -40 °C. The reaction mixture was allowed to stand until the temperature rose to 15 °C and then evaporated to dryness to give **3a-c** in almost quantitative yield. The crude product was recrystallized from a suitable solvent.

3a: mp 109-110 °C from CCl_4; 95 % yield; ^{1}H-nmr ($CDCl_3$): 4.78 (s, 2H, CH_2). *Anal.* Calcd for $C_{14}H_{10}N_3O_4ClS$: C, 47.81; H, 2.87; N, 11.95. Found: C, 47.66; H, 2.99; N, 11.80.

3b: mp 125-126 °C from CCl_4; 80 % yield; ^{1}H-nmr ($CDCl_3$): 4.75 (s, 2H, CH_2). *Anal.* Calcd for $C_{14}H_9N_3O_4Cl_2S$: C, 43.54; H, 2.35; N, 10.88. Found: C, 43.39; H, 2.38; N, 10.65.

3c: mp 87-89 °C from CCl_4/petroleum ether (40-60 °C); 78 % yield; ^{1}H-nmr ($CDCl_3$): 4.74 (s, 2H, CH_2). *Anal.* Calcd for $C_{14}H_{10}N_2O_2Cl_2S$: C, 49.28; H, 2.96; N, 8.21. Found: C, 49.05; H, 3.01; N, 8.27.

Dimethyl 2-Arylthio-5-(4-nitrophenyl)-1*H*-pyrrole-3,4-dicarboxylates (5a-c)

General Procedure- A solution of NEt_3 (0.28 g, 2.8 mmol) in benzene (10 ml) was added, during 1 h, to a stirred solution of **3** (2.8 mmol) and dimethyl acetylenedicarboxylate (0.4 g, 2.8 mmol) in benzene (40 ml). The resulting mixture was stirred for an additional hour and then transferred to a separatory funnel and washed with 30 ml of

water. The organic layer was dried over $MgSO_4$ and then evaporated to dryness. The residue was dissolved in hot ethanol (80 ml) and decolourized with charcoal. The resulting solution was concentrated to 20 ml and cooled. Compound **5** crystallized and was collected by filtration.

5a: 50 % yield; ir (KBr): 3511, 1722, 1695 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 9.80 (br s, 1H, NH), 3.80 (s, 3H, CH_3), 3.74 (s, 3H, CH_3). This compound melted at about 115 °C and immediately resolidified giving a different crystalline form: mp 181-182 °C; ir (KBr): 3253, 1736, 1692 cm^{-1}. The ir spectra in $CHCl_3$ and the ^{1}H-nmr spectra in $CDCl_3$ of the two crystalline forms were superimposable. *Anal.* Calcd for $C_{20}H_{15}N_3O_8S$: C, 52.52; H, 3.31; N, 9.19. Found: C, 52.37; H, 3.39; N, 9.27.

5b: 52 % yield; ir (KBr): 3516, 1720, 1693 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 9.20 (br s, 1H, NH), 3.82 (s, 3H, CH_3), 3.75 (s, 3H, CH_3). This compound melted at about 110 °C and immediately resolidified giving a different crystalline form: mp 203-204 °C; ir (KBr): 3155, 1712 cm^{-1}. The ir spectra in $CHCl_3$ and the ^{1}H-nmr spectra in $CDCl_3$ of the two crystalline forms were superimposable. *Anal.* Calcd for $C_{20}H_{14}N_3O_8ClS$: C, 48.84; H, 2.87; N, 8.55. Found: C, 48.74; H, 2.95; N, 8.40.

5c: mp 177-178 °C; 40 % yield; ^{1}H-nmr (DMSO-d_6): 10.71 (br s, 1H, NH), 4.46 (s, 3H, CH_3), 4.42 (s, 3H, CH_3); ir (KBr): 3306, 1640 cm^{-1}. *Anal.* Calcd for $C_{20}H_{15}N_2O_6ClS$: C, 53.76; H, 3.39; N, 6.27. Found: C, 53.87; H, 3.28; N, 6.39.

Ethyl 2-Arylthio-4(5)-(4-nitrophenyl)-1*H*-imidazole-5(4)-carboxylates (6a-c)

General Procedure- A solution of NEt_3 (0.28 g, 2.8 mmol) in benzene (10 ml) was added during 1 h to a stirred solution of **3** (2.8 mmol) and ethyl cyanoformate (1.39 g, 14 mmol) in benzene (50 ml), maintaining the temperature at 60 °C. The resulting mixture was stirred at 60 °C for an additional hour and then cooled, transferred to a separatory funnel and washed with 30 ml of water. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was stirred with a little ether, filtered and recrystallized from acetone to give **6**.

6a: mp 231-233 °C; 48 % yield; ^{1}H-nmr (DMSO-d_6): 10.52 (br s, 1H, NH), 4.21 (q, J = 7 Hz, 2H, CH_2), 1.16 (t, J = 7 Hz, 3H, CH_3); ir (KBr): 3263, 1677 cm^{-1}. *Anal.* Calcd for $C_{18}H_{14}N_4O_6S$: C, 52.17; H, 3.41; N, 13.52. Found: C, 51.97; H, 3.57; N, 13.64.

6b: mp 228-230 °C; 50 % yield; ^{1}H-nmr ($CDCl_3$): 10.78 (br s, 1H, NH), 4.36 (q, J = 7 Hz, 2H, CH_2), 1.25 (t, J = 7 Hz, 3H, CH_3); ir (KBr): 3280, 1673 cm^{-1}. *Anal.* Calcd for $C_{18}H_{13}N_4O_6ClS$: C, 48.17; H, 2.92; N, 12.48. Found: C, 48.30; H, 2.78; N, 12.40.

6c: mp 231-233 °C; 38 % yield; ^{1}H-nmr ($CDCl_3$): 10.78 (br s, 1H, NH), 4.40 (q, J = 7 Hz, 2H, CH_2), 1.38 (t, J = 7 Hz, 3H, CH_3); ir (KBr): 3279, 1665 cm^{-1}. *Anal.* Calcd for $C_{18}H_{14}N_3O_4ClS$: C, 53.54; H, 3.50; N, 10.41. Found: C, 53.62; H, 3.38; N, 10.30.

Dimethyl 2-[2-(Arylthio)-3,4-di(methoxycarbonyl)-5-(4-nitrophenyl)pyrrol-1-yl]maleates (7a-c)

General procedure- These compounds were obtained following the procedure described for the synthesis of

compounds (**5a-c**) except that a molar *ratio* **3** : dimethyl acetylenedicarboxylate = 1 : 5 was employed and the reaction was performed maintaining the temperature at 50 °C.

7a: mp 172-173 °C from acetone; 40% yield; ir (KBr): 1727 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 3.72, 3.65, 3.60, 3.53(4s, 12H, 4CH_3). *Anal.* Calcd for $C_{26}H_{21}N_3O_{12}S$: C, 52.09; H, 3.53; N, 7.01. Found: C, 52.15; H, 3.37; N, 6.88.

7b: mp 208-210 °C from acetone; 51% yield; ir (KBr): 1725 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 3.73, 3.65, 3.63, 3.54(4s,12H, 4CH_3). *Anal.* Calcd for $C_{26}H_{20}N_3O_{12}ClS$: C, 49.26; H, 3.18; N, 6.63. Found: C, 49.09; H, 3.28; N, 6.51.

7c: mp 144-146 °C from EtOH/i-Pr_2O; 42% yield; ir (KBr): 1728 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 3.78, 3.62, 3.60, 3.49(4s,12H, 4CH_3). *Anal.* Calcd for $C_{26}H_{21}N_2O_{10}ClS$: C, 53.02; H, 3.60; N, 4.76. Found: C, 53.22; H, 3.50; N, 4.61.

X-ray Crystallographic Data

$C_{26}H_{20}N_3O_{12}ClS$, molecular weight = 633.97, crystallizes in the monoclinic system, space group $P2_1/c$ with a = 17.891(6), b = 8.240(7), c = 20.190(12) A; β = 110.56(4)^0; z = 4; V = 2787(40) A^3; μ = 2.74 cm^{-1}; D_c = 1.51 g cm^{-3}; 4052 reflections were collected on an Enraf-Nonius CAD4 automatic diffractometer in the range $5 < 2\Theta < 45^o$, using Mo-Kα radiation (λ = 0.7107 A), Θ - 2Θ scan mode. The structure was solved by direct methods of SHELXS86 and refined by full-matrix least squares to R = 0.092, by using the 1491 observed reflections having $I > 3\sigma(I)$. The chlorine and sulfur atoms were refined anisotropically, whereas for the lighter atoms were used isotropic temperature factors. The hydrogen atoms were introduced in calculated positions with an overall temperature factor U of 0.05. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England.

REFERENCES

1. R. Bossio, S. Marcaccini, and R. Pepino, *Tetrahedron Lett.*, 1986, **27**, 4643.
2. See for example: E. Kuehle, "The Chemistry of The Sulfenic Acids", Georg Thieme Verlag, Stuttgart, 1973, p. 57; E. Kuehle: Houben-Weyl, 4 th ed., Vol. IV, Georg Thieme Verlag, Stuttgart, 1983, p. 522; R. Schubart: Houben-Weyl, 4 th ed., Vol. XI/1, Georg Thieme Verlag, Stuttgart, 1985, p. 63.
3. I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem. Internat. Edit.*, 1965, **4**, 472.
4. M. H. Hubacher, *Org. Synth., Coll. Vol. II*, 1943, 455.
5. T. Zincke, *Liebigs Ann. Chem.*, 1918, **86**, 416.
6. M. B. Sparke, J. L. Cameron, and N. Karasch, *J. Am. Chem. Soc.*, 1953, **75**, 4907.

Received, 30th July, 1990