Polycyclic Azines. III (1). Synthesis of 3-Aminoimidazo[1,5-*a*]pyridine Derivatives by Cyclodesulfurization of *N'*-Substituted-*N*-(2-pyridylmethyl)thioureas with Dicyclohexylcarbodiimide (2,3)

J. Bourdais (4) and A.-Mohsen M. E. Omar***

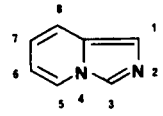
*Laboratoire de Chimie Hétérocyclique, Université Paris-Sud, Centre d'Orsay, 91405 Orsay, France, and
**Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Alexandria, Egypt

Received November 2, 1979

A series of 3-substituted aminoimidazo[1,5-*a*]pyridine derivatives have been synthesized by cyclodesulfurization of a variety of *N'*-substituted-*N*-(2-pyridylmethyl)thioureas with dicyclohexylcarbodiimide (DCCD). ^{1}H Nmr spectral analysis of all synthesized compounds is given.

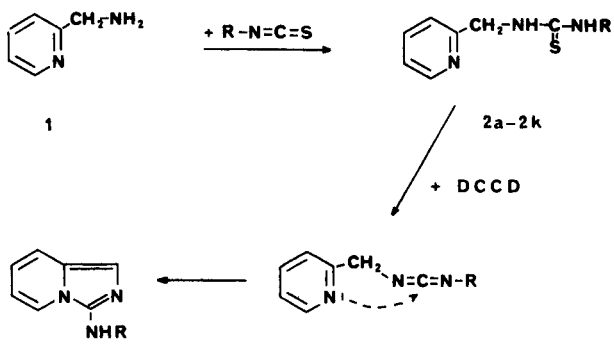
J. Heterocyclic Chem., **17**, 555 (1980).

The imidazo[1,5-*a*]pyridine ring system (I) is isomeric with benzimidazole. Thus, the 3-substituted amino[1,5-*a*]-pyridines (**3a-3k**, Scheme I) can be regarded as the nearest analogs of N^a-substituted benzimidazoles which are well known for their antiparasitic, fungicidal and herbicidal activities.



I

SCHEME I



a: R = CH_3 g: R = 2-Cl-C_6H_4

b: R = cyclohexyl h: R = 3-Cl-C_6H_4

c: R = C_6H_5-CH_2 i: R = 4-Cl-C_6H_4

d: R = C_6H_5 j: R = 4-CH_3O-C_6H_4

e: R = 3-F-C_6H_4 k: R = 2-naphtyl

f: R = 4-F-C_6H_4

The study of these types of compounds has been reported only once in the synthesis of some 3-acylamino-1-phenylimidazo[1,5-*a*]pyridines (5). To provide additional examples, we planned to investigate the preparation of a group of 3-alkyl, aryl and aralkylaminoimidazo[1,5-*a*]-pyridines (**3a-3k**, Scheme I). This involved the cyclo-desulfurization of various *N'*-substituted-*N*-(2-pyridyl-methyl)thioureas **2a-2k** with DCCD in accordance with the method recently established for the synthesis of a variety of azole (6) and benzotriazepinone (2) derivatives. The cyclodesulfurization of the thioureas **2a-2k** with DCCD provides a much more facile method than the one reported (5) for the synthesis of imidazo[1,5-*a*]pyridine derivatives.

The *N'*-substituted-*N*-(2-pyridylmethyl)thioureas **2a-2k** were prepared by reacting 2-aminomethylpyridine (**1**) with the appropriate alkyl, aryl or aralkylisothiocyanic ester in benzene at 20-50°. They were identified by elemental analysis, infrared (7) and pmr spectra (Table I). The cyclo-desulfurization of these thiourea derivatives could be achieved by refluxing with a 50% molar excess of DCCD in anhydrous benzene or toluene, and the cyclized 3-alkyl, aryl and aralkylaminoimidazo[1,5-*a*]pyridines **3a-3k** were obtained generally in good yields (Table II).

The rate of the cyclodesulfurization reactions was found to be dependant on the nature of the *N'*-substituents in the thioureas utilized. It was fast for the *N'*-aryl and very slow for the *N'*-alkyl substituents. As reported before in similar cyclization reactions (6) and by analogy with the synthesis of stable carbodiimides from thioureas and DCCD (8), this reaction is assumed to be proceeding *via* the carbodiimide intermediate **4** (Scheme I). Since the latter could never be isolated nor characterized by thin layer chromatography we believe that its formation from the thioureas **2** and DCCD is much slower than its ring closure to the imidazo-[1,5-*a*]pyridines **3**. Thus, this first step of the reaction seems to be the limiting one, leading to the very different rates which we have observed for this series of thiourea derivatives.

0022-152X/80/030555-04$02.25

Table I

Physical, Analytical and ^{1}H Nmr Spectral Data of *N'*-Substituted-*N*-(2-pyridylmethyl)thioureas **2a-k**

No.	M.p. °C (Crystallization Solvent)	Yield %	Formula	Analyses: Calcd./Found% C	H	N	^{1}H Nmr Spectral Data (a)
2a	144 (10,11) (Ethanol)	52	$C_8H_{11}N_3S$	53.03 53.24	6.12 5.97	23.19 23.48	(c): 3.00 (d, 3H, CH_3), 4.82 (d, 2H, CH_2), 7.24 (m, 1H, H-5), 7.34 (m, 1H, H-3), 7.70 (m, 1H, H-4), 8.50 (m, 1H, H-6), 7.5 (2 NH)
2b	109 (10) (CCl_4)	87	$C_{13}H_{19}N_3S$	62.62 62.53	7.68 7.56	16.86 17.20	(b): 1.0-2.2 and 4.0 (m, 11H, C_6H_{11}), 4.71 (d, 2H, CH_2), 7.24 (m, 1H, H-5), 7.30 (m, 1H, H-3), 7.69 (m, 1H, H-4), 8.49 (m, 1H, H-6), 7.3-7.7 (2 NH)
2c	118 (Ethyl Acetate)	67	$C_{14}H_{15}N_3S$	65.35 65.12	5.88 5.84	16.33 16.48	(b): 4.7 (d, 4H, 2(CH_2)), 7.3 (s, 5H, Ph), 7.2 (m, 1H, H-5), 7.3 (m, 1H, H-3), 7.67 (m, 1H, H-4), 8.35 (m, 1H, H-6), 7.7 (2 NH)
2d	112 (Benzene)	80	$C_{13}H_{13}N_3S$	64.18 64.35	5.39 5.47	17.28 17.50	(b): 4.93 (d, 2H, CH_2), 7.3-7.5 (m, 5H, Ph), 7.16 (m, 1H, H-5), 7.3 (m, 1H, H-3), 7.65 (m, 1H, H-4), 8.40 (m, 1H, H-6), 7.85 (t, NH), 8.90 (s, N'H)
2e	132 (CCl_4)	88	$C_{13}H_{12}FN_3S$	59.76 59.85	4.63 4.87	16.08 16.18	(b): 4.92 (d, 2H, CH_2), 7.1-7.5 (m, 5H, Ar + H-3), 6.93 (m, 1H, H-5), 7.68 (m, 1H, H-4), 8.42 (m, 1H, H-6), 8.10 (t, NH), 9.14 (s, N'H)
2f	108 (Benzene)	95	$C_{13}H_{12}FN_3S$	59.76 59.96	4.63 4.95	16.08 16.23	(b): 4.90 (d, 2H, CH_2), 7.0-7.5 (m, 6H, Ar + H-3 + H-5), 7.66 (m, 1H, H-4), 8.38 (m, 1H, H-6), 7.82 (t, NH), 9.00 (s, N'H)
2g	136 (Benzene)	76	$C_{13}H_{12}ClN_3S$	56.22 56.46	4.35 4.47	15.13 15.30	(c): 4.93 (d, 2H, CH_2), 7.1-7.9 (m, 6H, Ar + H-3 + H-5), 7.70 (m, 1H, H-4), 8.50 (m, 1H, H-6), 8.28 (t, NH), 9.05 (s, N'H)
2h	152 (Benzene)	62	$C_{13}H_{12}ClN_3S$	56.22 55.98	4.35 3.58	15.13 15.36	(c): 4.92 (d, 2H, CH_2), 7.0-7.8 (m, 7H, Ar + H-3 + H-4 + H-5), 8.54 (m, 1H, H-6), 8.25 (t, NH), 9.80 (s, N'H)
2i	142 (Ethyl Acetate)	65	$C_{13}H_{12}ClN_3S$	56.22 55.85	4.35 4.30	15.13 15.10	(b): 4.90 (d, 2H, CH_2), 7.35 (s, 4H, Ar), 7.2 (m, 1H, H-5), 7.3 (m, 1H, H-3), 7.68 (m, 1H, H-4), 8.40 (m, 1H, H-6), 7.95 (t, NH), 9.10 (s, N'H)
2j	154 (Ethanol)	94	$C_{14}H_{15}N_3OS$	61.53 61.32	5.53 5.55	15.38 15.13	(b): 3.80 (s, 3H, CH_3), 4.90 (d, 2H, CH_2), 6.9-7.4 (m, 6H, Ar + H-3 + H-5), 7.65 (m, 1H, H-4), 8.40 (m, 1H, H-6), 7.6 (t, NH), 8.4 (s, N'H)
2k	171 (Acetonitrile)	82	$C_{17}H_{15}N_3S$	69.61 69.33	5.15 5.01	14.33 14.52	(c): 4.93 (d, 2H, CH_2), 7.2-8.2 (m, 10H, Ar + H-3 + H-4 + H-5), 8.53 (m, 1H, H-6), 8.30 (t, NH), 9.96 (s, N'H)

(a) Nmr Solvent; (b): Deuteriochloroform, (c): Deuteriochloroform/10% DMSO-d_6.

Owing to their basic properties, the 3-aminoimidazo-[1,5-*a*]pyridine derivatives **3a-3k** could easily be separated from the dicyclohexylthiourea formed upon washing their mixture with dilute aqueous hydrochloric acid. In general, most of the rather unstable cyclized products were isolated and purified as free bases. Compounds **3a** and **3c** were best characterized as their picric acid salts. The confirmation of structure was accomplished by elemental analysis, infrared and pmr spectra.

The pmr spectra of the *N'*-substituted-*N*-(2-pyridylmethyl)thioureas **2a-2k** exhibited four multiplets at 7.3, 7.7, 7.2 and 8.4 ppm for the H-3, H-4, H-5 and H-6 protons, respectively, of the pyridine ring. In addition, the N-H proton attached to pyridine part of the thioureas appeared as a triplet at 7.5-8.3 ppm, while that of the R-NH part showed as a singlet at 9.0-10.0 ppm. The 3-substituted aminoimidazo[1,5-*a*]pyridine derivatives showed a singlet for H-1 at 7.1-7.3 ppm and four multiplets at 7.5-7.9, 6.4-6.5, 6.5-6.7 and 7.2-7.4 ppm for the H-5, H-6, H-7 and H-8, respectively, of the imidazo[1,5-*a*]pyridine system (9). The signals for each individual compound are shown in Tables I and II.

EXPERIMENTAL

Melting points were determined on a Kofler bank. The ^{1}H nmr spectra were recorded on a Perkin-Elmer R-32 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) from TMS as the internal standard. Abbreviations: s = singlet, d = doublet, t = triplet and m = multiplet. The progress of all reactions and purity of products were checked by silica gel (F_{254} Merck) thin layer chromatography with

Table II

Physical, Analytical and ^{1}H Nmr Spectral Data of 3-Substituted Aminoimidazo[1,5-*a*]pyridines **3a-k**

No.	M.p. °C (Crystallization Solvent)	Yield %	Formula	Analyses: Calcd./Found% C	H	N	^{1}H Nmr Spectral Data (a)
3a (d)	200-205 dec. (Ethanol)	58	$C_{14}H_{12}N_6O_7$	44.68 44.36	3.21 3.34	22.34 22.05	(c): 3.16 (d, 3H, CH_3), 6.55 (m, 1H, H-6), 6.70 (m, 1H, H-7), 7.20 (m, 1H, H-8), 7.10 (s, 1H, H-1), 8.06 (m, 1H, H-5), 8.7 (s, NH), 8.75 (2H Ar)
3b	151-152 (Cyclohexane)	51	$C_{13}H_{17}N_3$	72.52 72.95	7.96 8.15	19.52 19.30	(b): 1.1-2.2 and 3.6 (m, 11H, C_6H_{11}), 3.6 (s, 1H, NH), 6.32 (m, 1H, H-6), 6.46 (m, 1H, H-7), 7.10 (s, 1H, H-1), 7.23 (m, 1H, H-8), 7.48 (m, 1H, H-5)
3c (d)	148-149 dec. (Ethyl Acetate)	32	$C_{20}H_{16}N_6O_7$	53.10 52.81	3.57 3.89	18.58 18.16	(c): 4.76 (d, 2H, CH_2), 6.56 (m, 1H, H-6), 6.75 (m, 1H, H-7), 7.17 (m, 1H, H-8), 7.35 (s, 1H, H-1), 8.20 (m, 1H, H-5), 7.35 and 8.70 (7H Ar), 8.8 (s, 1H, NH)
3d	182 (Benzene)	65	$C_{13}H_{11}N_3$	74.62 74.40	5.30 5.29	20.08 19.88	(c): 6.42 (m, 1H, H-6), 6.59 (m, 1H, H-7), 7.20 (s, 1H, H-1), 7.33 (m, 1H, H-8), 6.7-7.2 (m, 5H, Ar), 7.95 (m, 1H, H-5), 8.3 (s, 1H, NH)
3e	168 (Ethyl Acetate)	82	$C_{13}H_{10}FN_3$	68.70 68.57	4.43 4.43	18.50 18.38	(b): 6.3-6.8 (m, 5H, Ar + H-6 + H-7), 7.05 (m, 1H, Ar), 7.2 (s, 1H, NH), 7.33 (s, 1H, H-1), 7.40 (m, 1H, H-8), 7.61 (m, 1H, H-5)
3f	180 (Ethyl Acetate)	75	$C_{13}H_{10}FN_3$	68.70 69.01	4.43 4.61	18.50 18.36	(b): 6.4-7.0 (m, 7H, Ar + H-6 + H-7 + NH), 7.28 (s, 1H, H-1), 7.38 (m, 1H, H-8), 7.60 (m, 1H, H-5)
3g	140 (Ethyl Acetate)	80	$C_{13}H_{10}ClN_3$	64.07 64.11	4.14 4.14	17.24 17.47	(b): 6.4-7.2 (m, 6H, Ar + H-6 + H-7 + NH), 7.35 (s, 1H, H-1), 7.4 (m, 1H, Ar), 7.43 (m, 1H, H-8), 7.60 (m, 1H, H-5)
3h	178 (Ethyl Acetate)	77	$C_{13}H_{10}ClN_3$	64.07 63.70	4.14 4.13	17.24 17.38	(b): 6.4-7.2 (m, 7H, Ar + H-6 + H-7 + NH), 7.35 (s, 1H, H-1), 7.42 (m, 1H, H-8), 7.60 (m, 1H, H-5)
3i	194-195 dec. (Ethyl Acetate)	70	$C_{13}H_{10}ClN_3$	64.07 63.84	4.14 4.36	17.24 17.30	(c): 6.47 (m, 1H, H-6), 6.61 (m, 1H, H-7), 7.20 (s, 1H, H-1), 7.20 (s, 4H, Ar), 7.35 (m, 1H, H-8), 7.90 (m, 1H, H-5), 8.6 (s, 1H, NH)
3j	160-161 (Ethyl Acetate)	53	$C_{14}H_{13}N_3O$	70.27 70.53	5.48 5.50	17.56 17.67	(b): 3.72 (s, 3H, CH_3), 6.38 (m, 1H, H-6), 6.57 (m, 1H, H-7), 6.5-6.8 (m, 5H, Ar + NH), 7.27 (s, 1H, H-1), 7.35 (m, 1H, H-8), 7.63 (m, 1H, H-5)
3k	237-238 (Acetonitrile)	58	$C_{17}H_{13}N_3$	78.74 79.06	5.05 5.23	16.21 16.46	(c): 6.47 (m, 1H, H-6), 6.64 (m, 1H, H-7), 7.1-7.8 (m, 8H, Ar + H-8), 7.26 (s, 1H, H-1), 7.93 (m, 1H, H-5), 8.6 (s, 1H, NH)

(a) Nmr Solvent: (b): Deuteriochloroform, (c): Deuteriochloroform/10% DMSO-d_6. (d) Picric Acid Salts.

ultraviolet light and iodine vapor for detection purposes. Except for 4-methoxyphenyl isothiocyanate, all the starting isothiocyanic esters were commercially available.

General Procedure for the Preparation of *N'*-Substituted-*N*-(2-pyridylmethyl)thioureas **2**.

N'-(4-Methoxyphenyl)-*N*-(2-pyridylmethyl)thiourea (**2j**), as an Example.

A solution of 2-aminomethylpyridine (**1**) (5.4 g., 0.05 mole) in anhydrous benzene (50 ml.) was stirred at 20°, and a solution of 4-methoxyphenyl isothiocyanate (8.25 g., 0.05 mole) in benzene (30 ml.) was added dropwise during 20 minutes. The mixture was stirred at 50-60° for 10 minutes and the solvent evaporated *in vacuo*. The residue was washed with petroleum ether and dried to give 13.5 g. (99%) of almost pure **2j**, m.p. 153°. The product was crystallized from ethanol, m.p. 154°. (Table I).

General Procedure for the Cyclodesulfurization of the Thioureas **2** into the 3-Substituted Aminoimidazo[1,5-*a*]pyridines **3** with DCCD.

A solution of the thiourea **2a-2k** (0.01 mole) and DCCD (0.015 mole) in anhydrous benzene (25 ml.) (or anhydrous toluene for **2c**, acetonitrile for **2a**) was heated under reflux, under a nitrogen atmosphere, for 1-3 hours (7 hours for **2c**, and 3 days for **2a** and **2b**), while checking the completion of reaction by tlc. The solvent was evaporated *in vacuo* and the residue extracted with chloroform and 4% aqueous hydrochloric acid solution (30 ml.). The acidic layer was neutralized with aqueous potassium carbonate solution to liberate the cyclized product **3a-3j**. The insoluble hydrochloric salt of **3k** was obtained by heating on the water-bath, and afforded the free base **3k** after treatment with potassium carbonate. Compounds **3b** and **3d-3k** were crystallized from the appropriate solvent (Table II), while compounds **3a** and **3c** were converted into the corresponding picric acid salts.

Other picric acid salts that were prepared from the pure bases **3** are below.

3-Phenylaminoimidazo[1,5-*a*]pyridine Picrate (**3d**).

This compound had m.p. 170-172°, dec. (dark yellow plates from ethyl acetate).

Anal. Calcd. for $C_{19}H_{14}N_6O_7$: C, 52.06; H, 3.22; N, 19.17. Found: C, 52.21; H, 3.40; N, 19.37.

3-(3-Fluorophenylamino)imidazo[1,-5*a*]pyridine Picrate (**3e**).

This compound had m.p. 160-162°, dec. (dark yellow parallelepipeds from acetonitrile).

Anal. Calcd. for $C_{19}H_{13}FN_6O_7$: C, 50.00; H, 2.88; N, 18.42. Found: C, 50.37; H, 3.04; N, 18.37.

3-(2-(Chlorophenylamino)imidazo[1,5-*a*]pyridine Picrate (**3g**).

This compound had m.p. 172-174°, dec. (yellow parallelepipeds from acetonitrile).

Anal. Calcd. for $C_{19}H_{13}ClN_6O_7$: C, 48.26; H, 2.77; N, 17.78. Found: C, 48.21; H, 3.02; N, 17.87.

3-(3-Chlorophenylamino)imidazo[1,5-*a*]pyridine Picrate (**3h**).

This compound had m.p. 195-198°, dec. (dark yellow plates from acetonitrile).

Anal. Calcd. for $C_{19}H_{13}ClN_6O_7$: C, 48.26; H, 2.77; N, 17.78. Found: C, 48.33; H, 3.22; N, 17.95.

3-(2-Naphthylamino)imidazo[1,5-*a*]pyridine Picrate (**3k**).

This compound had m.p. 138-140°, dec. (microcristals from acetonitrile).

Anal. Calcd. for $C_{23}H_{16}N_6O_7$: C, 56.56; H, 3.30; N, 17.21. Found: C, 56.21; H, 3.44; N, 17.15.

Acknowledgement.

The authors wish to acknowledge the assistance of Mr. E. Dorme and his staff for the microanalyses, Mrs. Y. Cabaret for the pmr spectra and Mr. M. Pelleterat for a part of the syntheses.

REFERENCES AND NOTES

(1) Previous papers regarded as Parts I and II are respectively: J. Bourdais, D. Abenhaim, B. Sabourault and A. Lorre, *J. Heterocyclic Chem.*, **13**, 491 (1976).; Ph. Gayral, J. Bourdais, A. Lorre and D. Abenhaim, *Eur. J. Med. Chem.-Chim. Ther.*, **13**, 171 (1978).

(2) This paper constitutes Part XVIII of the Series "The cyclodesulfurization of Thio Compounds". Part XVII: A.-Mohsen M. E. Omar, F. A. Ashour and J. Bourdais, *J. Heterocyclic Chem.*, **16**, 1435 (1979).

(3) A preliminary account of this work was presented at the VIth Symposium on Chemistry of Heterocyclic Compounds, Brno, Czechoslovakia, July 4-7, 1978 (poster presentation).

(4) To whom all correspondence should be addressed.

(5) T. Irikura, K. Kasuga, T. Hashizume, M. Ohashi and M. Yamada, Japanese Patent 72 30,693, 9 Nov. 1972; *Chem. Abstr.*, **78**, 29,772z (1973).

(6) A.-Mohsen M. E. Omar, N. S. Habib and O. M. Aboulwafa, *Synthesis*, 864 (1977).

(7) A.-Mohsen, M. E. Omar and S. A. Osman, *Pharmazie*, **28**, 30 (1973).

(8) R. T. Wragg, *Tetrahedron Letters*, 3931 (1970).

(9) P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter and G. R. Underwood, *Aust. J. Chem.*, **17**, 1128 (1964).

(10) M. Yakushiji, K. Maeda and Y. Hirono, German Patent 2,548,898 (1976); *Chem. Abstr.*, **85**, 63,054w (1976).

(11) A. C. W. Curran, British Patent 1,461,806 (1977); *Chem. Abstr.*, **87**, 5309lh (1977).