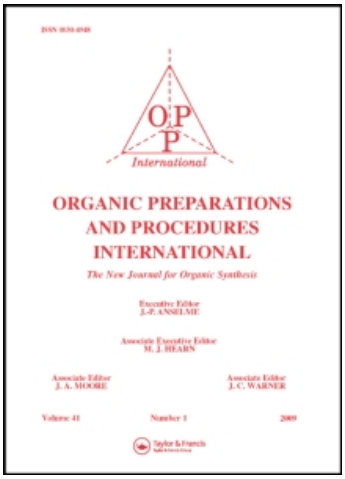


Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF NEW 5-CYANO AND 5-CARBAMOYLIMIDAZOLES FROM 5-NITROIMIDAZOLES BY PHOTOCYANATION

Michel P. Crozet[a]; Patrice Vanelle[ab]; Olivier Jentzer[a]; José Maldonado[ab]
[a] Laboratoire de Chimie Organique B, associé au CNRS UA 109, Marseille Cedex 13, FRANCE [b] Faculté de Pharmacie, Laboratoire de Chimie Organique, Marseille Cedex 4, FRANCE

To cite this Article Crozet, Michel P. , Vanelle, Patrice , Jentzer, Olivier and Maldonado, José(1989) 'PREPARATION OF NEW 5-CYANO AND 5-CARBAMOYLIMIDAZOLES FROM 5-NITROIMIDAZOLES BY PHOTOCYANATION', Organic Preparations and Procedures International, 21: 1, 105 — 108
To link to this Article: DOI: 10.1080/00304948909356352
URL: http://dx.doi.org/10.1080/00304948909356352

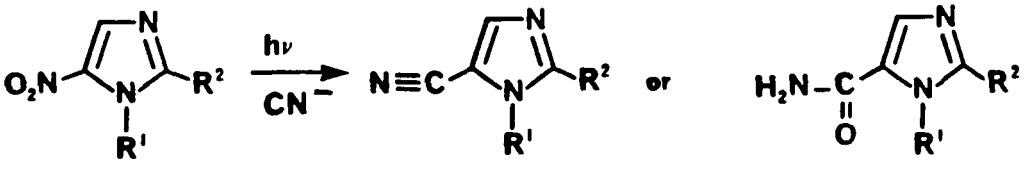
ORGANIC PREPARATIONS AND PROCEDURES INT. 21(1), 105-108 (1989)

PREPARATION OF NEW 5-CYANO AND 5-CARBAMOYLIMIDAZOLES FROM 5-NITROIMIDAZOLES BY PHOTOCYANATION

Michel P. Crozet* , Patrice Vanelle[§], Olivier Jentzer and José Maldonado[§]

Laboratoire de Chimie Organique B, associé au CNRS UA 109
13397 Marseille Cedex 13, FRANCE
[§]Laboratoire de Chimie Organique, Faculté de Pharmacie, 27 Bd J. Moulin
13885 Marseille Cedex 4, FRANCE

Since the introduction of metronidazole into therapy, 5-nitroimidazoles as a class of compounds have attracted much attention. These drugs are extensively used for the chemotherapy of anaerobic bacterial and protozoal diseases and also for the radiosensitization of hypoxic tumors.[1] Recent conflicting toxicological studies have revealed that many of these compounds have mutagenic or carcinogenic activities.[1,2] Thus, the search for new drugs is urgently needed even though a recent study has shown that it is possible to prepare non-mutagenic 5-nitroimidazoles.[3] An important current goal of heterocyclic chemistry is centered on the discovery of novel lead structures, without nitro groups, which, possibly after chemical design, exhibit an activity profile similar to that of metronidazole. As a part of a program directed toward the synthesis of modified 5-nitroimidazoles, we have extended the photoreaction of nitro aromatic and nitro heterocyclic compounds with cyanide ion[4] to



1 2 3

a) $R^1 = R^2 = CH_3$ b) $R^1 = CH_3$, $R^2 = CH_2OH$ c) $R^1 = CH_3$, $R^2 = CH_2Cl$ d) $R^1 = CH_3$, $R^2 = HC{=}C(CH_3)_2$ e) $R^1 = (CH_2)_2SO_2CH_2CH_3$, $R^2 = CH_3$ f) $R^1 = (CH_2)_3Cl$, $R^2 = CH_3$ g) $R^1 = CH_2CHOHCH_3$, $R^2 = CH_3$ h) $R^1 = (CH_2)_2OH$, $R^2 = CH_3$.

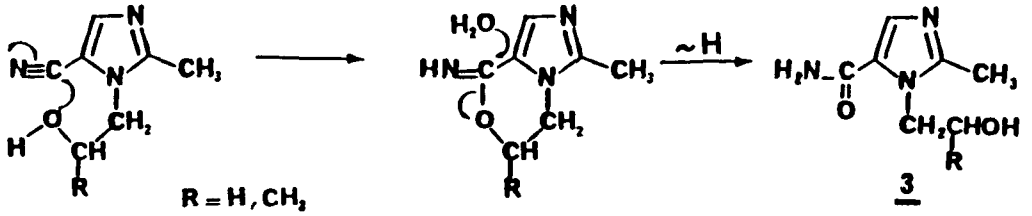
eight known 5-nitroimidazoles most of which are currently available as drugs and in wide use. Only the simplest 1-methyl-5-cyanoimidazole was reported[4] prior to this work.

All the compounds investigated are substituted at positions 1 and 2 with various alkyl or substituted alkyl groups and were subjected to irradiation with ultraviolet light in the presence of cyanide ion. The reaction proceeds in water and is photosensitized by acetone. The results are summarized in Table 1.

Table 1. 5-Cyano and 5-Carbamoylimidazoles from Photocyanation of 1.

Product	2a	2b	2c	2d	2e	2f	3g	3h
Yield (%)	82	30	37	38	78	71	48	55
Irr. time (hrs)	10	22	62	48	14	24	15	21

These nucleophilic photosubstitutions provide convenient and facile synthetic methods for the preparation of previously unknown 5-cyanoimidazoles 2. With 1g and 1h, the cyano group is hydrolysed in these reaction conditions ; a possible mechanism for the formation of the new 5-carbamoylimidazoles 3, involving intramolecular assistance by the hydroxyl group in the chain at position 1 is illustrated below.



All the new compounds gave satisfactory analytical and spectral data. Attempted photoreaction of dimetridazole 1a with other anions (phthalimide, thiocyanate, benzenesulfinate, thiophenate, fluoride and azide) was unsuccessful.

EXPERIMENTAL SECTION

Mps were determined in capillary tubes with a Bδchi apparatus and are

uncorrected. The ^{1}H-NMR spectra were recorded on a Varian 60 MHz spectrometer and the ^{13}C-NMR spectra on a Brucker 200 MHz instrument. Chemical shifts are reported in δ units (ppm) relative to internal TMS. An Ribermag R.10-10-C spectrometer was used for the mass spectra. Microanalyses were performed by the Ecole Supérieure de Chimie de Marseille. 1a, 1f, 1g, 1h were provided by Rhône-Poulenc Santé, 1e by Pfizer laboratories. The other compounds were obtained as described earlier.[5]

General Procedure.- A solution of 0.02 mole of 5-nitroimidazole, 3.4g of KCN (0.05 mole) and 300ml of water (or water/methanol (1/1) for 1d) containing 0.5ml of acetone was irradiated with a Hanau TQ 150 high pressure Hg lamp. During the reaction, the solution was stirred magnetically and kept at room temperature. After completion of the reaction, the solution was extracted with chloroform. The $CHCl_3$ layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The product was separated chromatographically on silica gel (eluent: $CHCl_3$/methanol (9/1)) and recrystallized from the appropriate solvent.

1,2-dimethyl-5-cyanoimidazole (2a), white solid (1.99 g, 82% yield), mp. (picrate) 211° (EtOH). ^{1}H NMR ($CDCl_3$) : δ 2.46 (s, 3H), 3.67 (s, 3H) , 7.47 (s, 1H).

Anal. Calcd. for $C_6H_7N_3$. $C_6H_3N_3O_7$ (picrate) : C, 41.15 ; H, 2.88 ; N, 23.99
Found : C, 41.11 ; H, 2.80 ; N, 24.01

1-methyl-2-hydroxymethyl-5-cyanoimidazole (2b), white solid (0.82 g, 30% yield), mp. 152° (ethyl acetate) ^{1}H NMR (DMSO-d_6) : δ 3.73 (s, 3H), 4.54 (d, 2H), 5.56 (t, 1H), 7.70 (s, 1H).

Anal. Calcd. for $C_6H_7N_3O$: C, 52.54 ; H, 5.14 ; N, 30.64
Found : C, 52.57 ; H, 5.16 ; N, 30.60

1-methyl-2-chloromethyl-5-cyanoimidazole (2c), orange yellow solid (1.15 g, 37% yield), mp. 38° (cyclohexane). ^{1}H NMR ($CDCl_3$) : δ 3.83 (s, 3H), 4.67 (s, 2H), 7.53 (s, 1H)

Anal. Calcd. for $C_6H_6ClN_3$: C, 46.32 ; H, 3.89 ; N, 27.01 ; Cl, 22.78
Found : C, 46.34 ; H, 4.10 ; N, 26.97 ; Cl, 22.80

1-methyl-2-isopropylidenemethyl-5-cyanoimidazole (2d), white solid (1.38 g, 38% yield), mp. 74° (cyclohexane). ^{1}H NMR ($CDCl_3$) : δ 1.96 (s, 3H), 2.14 (s, 3H), 3.63 (s, 3H), 5.93 (s, 1H), 7.60 (s, 1H). ^{13}C NMR ($CDCl_3$) 20.37, 27.03, 31.55, 104.95, 110.05, 111.73, 138.33, 147.63, 149.51.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06 ; H, 6.88 ; N, 26.00
Found : C, 67.01 ; H, 6.96 ; N, 25.96

1-(2-ethylsulfonyl)-2-methyl-5-cyanoimidazole (2e), white solid (3.55 g, 78% yield), mp. 89° (ethyl acetate). ^{1}H NMR ($CDCl_3$) : δ 1.40 (t, 3H), 2.54

(s, 3H), 2.97 (q, 2H), 3.43 (t, 2H), 4.52 (t, 2H), 7.56 (s, 1H).

Anal. Calcd. for $C_9H_{13}N_3O_2S$: C, 47.56 ; H, 5.76 ; N, 18.49 ; S, 14.11
Found : C, 47.57 ; H, 5.67 ; N, 18.55 ; S, 13.99

1-(3-chloropropyl)-2-methyl-5 cyanoimidazole (2f), yellow solid (2.61 g, 71% yield), mp. (picrate) 108-109° (95% EtOH). ^1H NMR (DMSO-d_6) : δ 2.06-2.43 (m, 2H), 2.51 (s, 3H), 3.53 (m, 2H), 4.22 (t, 2H), 7.57 (s, 1H).

Anal. Calcd. for $C_8H_{10}ClN_3 . C_6H_3N_3O_7$ (picrate) :
C, 40.74 ; H, 3.17 ; N, 20.36 ; Cl, 8.59
Found : C, 40.75 ; H, 3.19 ; N, 19.88 ; Cl, 8.50

1-(2-methyl-5-carbamoyl-1-imidazolyl)-2-propanol (3g), white solid (1.42 g, 48% yield), mp. 197° (diethyl ether). ^1H NMR ($CDCl_3$) : δ 1.50 (d, 3H), 2.40 (s, 3H), 3.93 (d, 2H), 4.12-4.74 (m, 3H), 7.55 (s, 1H).

Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.45 ; H, 7.15 ; N, 22.93
Found : C, 52.46 ; H, 7.13 ; N, 22.87

2-(2-methyl-5-carbamoyl-1-imidazolyl)-1-ethanol (3h), white solid (1.69 g, 55% yield), mp. 227° (water). ^1H NMR (DMSO-d_6) : δ 2.33 (s, 3H), 3.57 (q, 2H), 4.27 (t, 2H), 4.90 (t, 1H), 7.10-7.60 (m, 2H), 7.47 (s, 1H).

MS : M^+ = 169 ; m/e : 169 (37.2), 151 (56.4), 125 (55.3), 109 (100), 54 (55.3), 53 (46.8), 45 (26.6), 44 (29.8), 39 (10.6), 31 (27.6), 28 (46.8), 27 (40.4), 18 (14.9), 15 (12.7).

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.70 ; H, 6.55 ; N, 24.84
Found : C, 49.67 ; H, 6.47 ; N, 24.91

Acknowledgements.- We thank Professor Jean-Marie Surzur for helpful discussions, the Centre National de la Recherche Scientifique and the Groupe Rhône-Poulenc for financial support.

REFERENCES

1. C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tchelitcheff and R. Vaupré, Arzneim-Forsch., 16, 23 (1966) ; E. D. Erslager, "Medicinal Chemistry", Vol. 1, p. 522, A. Burger, Ed., Wiley-Interscience, New-York, 1970 ; A. Breccia, B. Cavalleri and G. E. Adams, "Nitroimidazoles : Chemistry, Pharmacology and Clinical Application", Plenum Press, New-York, 1982 ; M. D. Nair and K. Nagarajan, "Progress in Drug Research", Vol. 27, p.163, E.Jucker, Ed., Birkhauser Verlag, Basel, 1983.
2. R. N. Brogden, R. C. Heel, T. M. Speight and G. S. Avery, Drugs, 16, 387 (1978).
3. J. S. Walsh, R. Wang, E. Bagan, C. C. Wang, P. Wislocki and G. T. Miwa, J. Med. Chem., 30, 150 (1987).
4. J. Cornelisse, E. Havinga, Chem. Rev., 75, 353 (1975) ; C. Oldenhof and J. Cornelisse, Rec. Trav. Chim. Pays-Bas, 97, 35 (1978).
5. M. P. Crozet, J.-M. Surzur, P. Vanelle, C. Ghiglione and J. Maldonado, Tetrahedron Lett., 26, 1023 (1985).

(Received December 16, 1987; in revised form October 20, 1988)