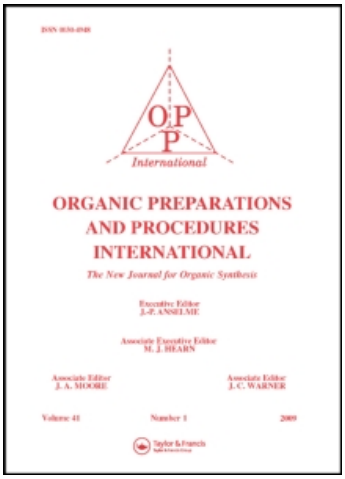


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 1-METHYL-2-TRICHLOROACETYLIMIDAZOLE

Elżbeta Masiukiewicz[a]; Damian Mrugala[a]; Barbara Rzeszotarska[a]
[a] Institute of Chemistry, University of Opole, Opole, POLAND

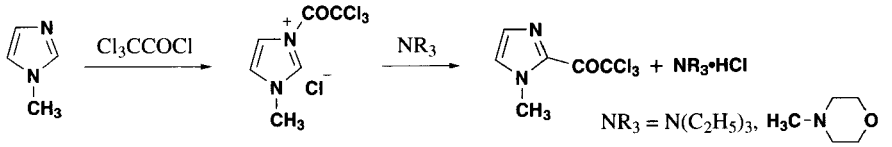
To cite this Article Masiukiewicz, Elżbeta , Mrugala, Damian and Rzeszotarska, Barbara(2005) 'AN IMPROVED SYNTHESIS OF 1-METHYL-2-TRICHLOROACETYLIMIDAZOLE', Organic Preparations and Procedures International, 37: 4, 403 — 405
To link to this Article: DOI: 10.1080/00304940509354973
URL: http://dx.doi.org/10.1080/00304940509354973

AN IMPROVED SYNTHESIS OF 1-METHYL-2-TRICHLOROACETYLIMIDAZOLE

Submitted by Elżbieta Masiukiewicz, Damian Mrugała and Barbara Rzeszotarska*
(05/06/05)

Institute of Chemistry, University of Opole
Ul. Oleska 48, 45-052 Opole, POLAND
e-mail: rzeszot@uni.opole.pl

Lexitropsins, the oligoamides of some *N*-methylheteroaromatic amino acids, *viz.* of those derived from *N*-methylpyrrole, *N*-methyl-3-hydroxypyrrole, *N*-methylimidazole and other *N*-methylhetarenes are so far the most promising structures for the regulation of gene expression in biotechnology.[1] It is known that the trichloroacetyl group of the title compound can be converted to the acid, esters or amides with facility.[2] Therefore this compound serves as the independent *N*-terminal component of oligoamides.[1,3] It is also useful as a substrate for the introduction of the amino group through nitration at position 4 and the reduction of the nitro group to the 4-amino group.[2,4,5] 1-Methyl-2-trichloroacetylimidazole is synthesized through the addition of trichloroacetyl chloride to *N*-methylimidazole in an organic solvent; after a waiting period of time for the formation of the salt triethylamine is added to complete the reaction.[2,6] During the addition of triethylamine, the reaction mixture grows dark and therefore the total time was kept to only one hour.[2] The product was isolated with the help of column chromatography. Because attempts to reproduce the literature procedure failed, we now report the elaboration of an improved preparation of 1-methyl-2-trichloroacetylimidazole.



The action of triethylamine turned out to be too brief to secure a good yield. The chromatographic column did not fully remove triethylamine hydrochloride, and experiments to purify the compound by other methods failed, because 1-methyl-2-trichloroacetylimidazole was too reactive and gave several decomposition by-products. During attempts to wash out the triethylamine hydrochloride with water, it was found that the triethylamine remained partially in the organic phase which brought about the decomposition of the compound. We thus have substituted triethylamine by *N*-methylmorpholine which is removed completely by washing with water and carried out the reaction under nitrogen. The reaction with *N*-methylmorpholine was performed for 20 hours. Upon evaporation of the solvents, diethyl ether was added to the residue to remove a small amount of an insoluble solid. Upon repeated evaporation, the product crystallized spontaneously. It was obtained in 88% yield and 100% purity by HPLC.

The improved method of the synthesis of 1-methyl-2-trichloroacetylimidazole displays a high degree of convenience and practicality, because it does require the use of a chromatography or re-crystallization. At room temperature, the compound is unstable and is hydrolyzed in moist air to 1-methylimidazole-2-carboxylic acid (a haloform reaction). Its 1% solution in dry dichloromethane is stable for two months; however, 1% addition of *N*-methylimidazole or triethylamine causes complete hydrolysis in several hours. 1-Methyl-2 trichloroacetylimidazol, kept at –30°C is stable for more than three months.

EXPERIMENTAL SECTION

Reactions were monitored and the products checked on a DC Alufolien Kieselgel 60 No 1.05553 Merck in the solvent system A (v/v): benzene-methanol-acetone-pyridine-acetic acid (24:4:2:2:1), visualization with chlorine–KI–tolidine, and on a DC Alufolien Kieselgel 60 F_{254} No 1.05553 Merck in the solvent system B (v/v): benzene-ethyl acetate (7:2) and in the solvent system C (v/v): chloroform-methanol-acetic acid (95:5:3), vizualization under an UV λ 254 nm lamp, and then with chlorine–KI–tolidine. The solvents from the reaction mixture were removed *in vacuo* on a rotary evaporator at a bath temperature not exceeding 30°C. HPLC analysis was carried out using a Beckman System Gold chromatograph, a 5 µL loop, an Alltech Alltima, C_{18}, 5 µm, 150 x 4.6 mm column, mobile phase: 0.1% aqueous trifluoroacetic acid-acetonitrile (85:15), a flow rate of 1 mL/min and detection at 210 nm. The IR spectrum was recorded on a Philips Analytical PU9800 FTIR spectrometer at 2 cm^{-1} nominal resolution. MS spectrum was taken on a MS 59 5973 (EI) mass spectrometer.

1-Methyl-2-trichloroacetylimidazole.- A stirred solution of trichloroacetyl chloride (11.2 mL, 100 mmol) in acetonitrile (100 mL) was cooled to –5°C, and purged with nitrogen for 15 min; then *N*-methylimidazole (8 mL, 100 mmoles) was added dropwise. After 1.5 h stirring, the temperature was raised to 20°C and stirring was continued for an hour. Then the reaction mixture was cooled to –5°C, *N*-methylmorpholine (10.4 ml, 95 mmoles) was added dropwise, stirring was continued for an hour and reaction mixture was left to stand at room temperature for 20 h. The solution was evaporated to half its volume and chloroform (100 mL) was added. The organic phase was extracted with water (3 x 50 mL) and brine (2 x 50 mL), dried and evaporated to give an orange crystalline solid. Diethyl ether (75 mL) was added, and after a minute, the flocculent precipitate which had formed, was filtered off. Evaporation of the straw-colored filtrate afforded 19.11 g (88%) of a light yellow crystalline solid, mp. 75-77°C (uncorrected, a Boëtius heating block), *lit.*[6] mp. 74°C, *lit.*[2] mp. 79-80°C. TLC: R_f (A) 0.76, R_f (B) 0.60, R_f (C) 0.70. HPLC: tR 7.57 min, 100% purity. FTIR (KBr): 3141, 3115, 2958, 1684, 1385 cm^{-1}, (CH_2Cl_2): 1700, 1389 cm^{-1}. MS m/z for $C_6H_5Cl_3N_2O$: 227 (M+, 31%), 109 (M–CCl_3, 100%), 82 (M–$COCCl_3$, 9%), 54 (M–$COCCl_3$–HC≡N, 15%).

Acknowledgement.- The work was financially supported by a grant-in-aid from the Polish State Committee for Scientific Research 1/ICh-S-2005. The support deserves our grateful thanks.

REFERENCES

1. P. B. Dervan and B. S. Edelson, *Curr. Opin. Struct. Biol.*, **13**, 284 (2003) and reference therein.

2. E. Nishiwaki, S. Tanaka, H. Lee and M. Shibuya, *Heterocycles,* **27**, 1945 (1988).

3. J. Xiao, G. Yuan, W. Huang, A. S. C. Chan and K.-L. D. Lee, *J. Org. Chem.*, **65**, 5506 (2000).

4. N. R. Wurtz, J. M. Turner, E. E. Baird and P. B. Dervan, *Org. Lett.* **3**, 1201 (2001).

5. M. A. Marques, R. M. Doss, A. R. Urbach and P. B. Dervan, *Helv. Chim. Acta*, **85**, 4485 (2002)

6. E. Regel and K-H. Büchel, *Liebigs Ann. Chem.*, 145 (**1977**).

****

FORMATION OF OXIRANES DURING THE PREPARATION OF AROYLACETONITRILES

Submitted by (05/06/05)

R. B. Toche*, M. N. Jachak, N. S. Badgujar, A. B. Avhale, and D. B. Kendre

Post Graduate Department of Chemistry, K. T. H. M. College
Gangapur Road, Nashik-422002, INDIA
e-mail: raghunath_toche@rediffmail.com

Some aroylacetonitriles have been shown to exhibit various biological activities[1-3] and are valuable precursors for the synthesis of a number of heterocyclic compounds.[3-9] Aroylacetonitriles have been prepared *via* S_N2 displacement of halide by cyanide.[3,8,9] The use of the literature method for the synthesis of aroylacetonitriles in our laboratory led to results somewhat different from those reported.[3,8,9] It was found that addition of an aqueous solution of NaCN or KCN to ethanolic solutions of α-chloro- or α-bromoacetophenones at room temperature with constant stirring resulted in an exothermic reaction (temperature rises to 40-50°C) and precipitation of a solid in each case. These solids turned out to be different than the expected and known aroylacetonitriles derived from the normal displacement reaction.