Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile High Yielding Method for Synthesis of N-Alkyl-4-Nitroimidazoles

A. K. S. Bhujanga Rao [a] , C. Gundu Rao [a] & B. B. Singh [a]
[a] R&D Centre, Reckitt & Colman of India Limited, Plot 176, SIPCOT Industrial Complex, Hosur, 635 126, Tamil Nadu, India
Published online: 24 Sep 2006.

To cite this article: A. K. S. Bhujanga Rao , C. Gundu Rao & B. B. Singh (1991) A Facile High Yielding Method for Synthesis of N-Alkyl-4-Nitroimidazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:3, 427-433, DOI: 10.1080/00397919108016766

To link to this article: http://dx.doi.org/10.1080/00397919108016766

SYNTHETIC COMMUNICATIONS, 21(3), 427-433 (1991)

A FACILE HIGH YIELDING METHOD FOR SYNTHESIS OF N-ALKYL-4-NITROIMIDAZOLES

A K S Bhujanga Rao, C Gundu Rao and B B Singh*

R&D Centre, Reckitt & Colman of India Limited,
Plot 176, SIPCOT Industrial Complex,
Hosur-635 126, Tamil Nadu, India

Abstract : A high yielding and fast reaction for the synthesis of a variety of N-alkyl 4-nitroimidazoles has been described. This method involves reaction of 2-methyl-4(5)-nitro-1H-imidazole with suitable alkyl halides in K_2CO_3/DMF at 110-120°C.

N-alkyl nitroimidazoles are important intermediates for the synthesis of chemotherapeutic agents and potential biocides for agricultural use. Metronidazole and Tinidazole synthesized from 2-methyl-5-nitroimidazole by suitable N^1-alkylation have been widely used in the treatment of protozoal infections like trichomoniasis.[1,2] The N-alkylated 4-nitroimidazoles have been gaining pharmacological significance and show great potential as immunosuppresants, aldehyde dehydrogenase inhibitors, radiosensitizers and radiotherapy synergists.[3-6]

The N-alkylation of nitroimidazoles is normally carried out by its condensation with suitable alkyl halides, sulfates or tosylates. Most of these methods invariably result in a

* To whom correspondence should be addressed.

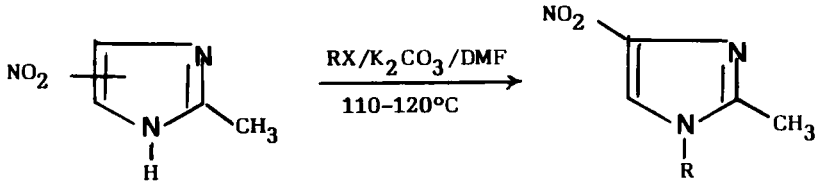
mixture of 4-nitro and 5-nitro isomers of the N-alkylated product, the ratio of isomers being dependent upon the reaction conditions. It has been observed that the acidic conditions favour the formation of 5-nitroisomers and basic conditions 4-nitroisomer.[7,8] The yields reported in literature by using these methods are generally low except for one report where high yield (84%) of 1-benzyl-2-methyl-4-nitro imidazole has been obtained by reaction of 2-methyl-4-nitro imidazole with benzyl bromide.[9] Some recent methods reported for N-alkylation also suffer from the short comings like low yields and complicated reaction procedures.[10,11] These methods require use of either tetraalkyl ammonium salts of nitroimidazoles or special reagents like alkoxy phosphonium salts.

We have recently reported a method for preparation of N-substituted 4-nitro-1H-imidazoles in near quantitative yields.[12, 13] Since this method involves addition of nitroimidazole to a Michael acceptor, the N-alkylated product is always the one where alkyl group carries a functional group. This method, thus, has a limitation that it cannot be used for the synthesis of compounds with simple N-alkyl groups.

We now report here a simple and facile method for synthesis of N-alkyl 4-nitroimidazoles in excellent yields. In some cases yields are near quantitative. This method involves the reaction of 4(5)-nitroimidazole with suitable alkyl

chloride or bromide at elevated temperatures (110-120°C) in K_2CO_3/DMF for a period of 2-3 h. The N-alkylation of 2-methyl 4(5)-nitroimidazole with a variety of alkyl halides has been carried out using this method giving excellent yields which are presented in the table.

TABLE



Sl. No.	Alkylating Agent RX	Time h	Yield %
1	C_2H_5Br	3	87
2	Pr^nBr	3	84
3	Bu^nBr	3	85
4	$CH_2=CH-CH_2Br$	2	92
5		3	83
6	$C_6H_5.CH_2Cl$	2	94
7	$(p)Cl-C_6H_4-CH_2Cl$	2	95

The example 6, from the above table illustrates the superiority of this method. As compared with the best yield of 84% reported in literature with an expensive chemical, benzyl bromide, the yield of 94% reported here has been obtained with a much cheaper material, benzyl chloride, just in 2 h as against literature report of 18 h.[9]

EXPERIMENTAL

Typical Procedures

1-Benzyl-2-Methyl-4-Nitroimidazole

A mixture of 2-methyl-4(5)-nitroimidazole (12.7 g, 100 mmol), benzyl chloride (15.2 g, 120 mmol), potassium carbonate (20 g, 145 mmol) and dimethyl formamide (30 ml) was heated under stirring at 110-120°C for 2 h. The reaction mass was evaporated to dryness under reduced pressure, and the residue was partitioned between 50 ml water 50 ml ethyl acetate. The ethyl acetate extract was concentrated and the residue on crystallisation from ethyl acetate-hexane gave 20.4 g (94%) of the product. m.p.: 104-106°C (Lit.[9] m.p. 104-105°C), H^1NMR ($CDCl_3$): 2.40 (S,3,CH_3), 5.15 (S,2,-CH_2-), 7.05-7.50 (m,5,Ph), 7.65 (s,1,C_5-H), C_5-H $\Delta\delta$ (DMSO-d_6-$CDCl_3$) 0.55.

1-(Cyclopropyl methyl)-2-Methyl-4-Nitroimidazole

A mixture of 2-methyl-4(5)-nitroimidazole (5.19 g, 40 mmol), cyclopropylmethylbromide (6.5 g, 48 mmol), anhydrous potassium carbonate (8 g, 58 mmol) and dimethyl formamide (15 ml) was heated at 110-120°C for 3 h. Work-up was done as described in the previous example. Recrystallisation from ethyl acetate-hexane afforded 6.0 g (83%) of the product. m.p. : 77-79°C, ^1H NMR (DMSO-d_6), 0.30-0.80 (m,4,-CH_2-CH_2-), 1.3 (m,1,CH), 2.4 (s,3,CH_3), 3.9 (d,2,N-CH_2), 8.30 (s,1,C_5-H), C_5-H $\Delta\delta$ (DMSO-d_6-$CDCl_3$):0.60.

Acknowledgement

We thank Prof. K M Madyastha, Indian Institute of Science, Bangalore, for useful discussions and acknowledge the support from our analytical laboratory.

REFERENCES

1. Cosar, C; Julou, L. Ann.Inst.Pasteur (Paris) 1959, 96, 238.
2. Nord, C.E., J.Antimicrob. Chemother, 1982, 10 (Suppl.A35).
3. Galanaud, P., Pharmacologie Clinique. Bases de la therapeutique., Giroud, J.P., Mathe, G.; Meyniel, G.. Eds; Expansion Scientifique : Paris, 1978; p 1781-1795; Chem.Abstr. 1979, 90, 81101 s.
4. Klink, R.; Pachler, K.G.R.; Gottschlich, R. Arzneium.-Forsch. 1985, 35(8), 1220.
5. Morgenstern, J.; Otto, R.; Scheithauner, S. Ger(East) DD 260,062, 14 Sept 1988; Chem.Abstr. 1989, 110, 231634 r.
6. Chibber, R.; Stratford, I.J.; Ahmed, I.; Robbins, A.B.; Goodgame, D.; Lee, B. Int.J.Radiat.Oncol., Biol. Phys. 1984, 10, 1213.
7. Butler, K.; Howes, H.L.; Lynch, J.E.; Pirie, D.K. J.Med.Chem. 1967, 10, 891. Kajfez, F.; Sunjic, V.; Kolban, D.; Fajdiga, T.; Oklobdzija, M. J.Med.Chem. 1968, 11, 167. Kajfez, F.; Kolban, D.; Oklobdzija, M.; Fajdiga, T.; Slamnik, M.; Sunjic, V. Croat. Chem.

Acta 1967, 39, 199. Cavalleri, B. Nitroimidazole Chemistry, Synthetic Methods in Nitroimidazoles. Chemistry, pharmacology and chemical applications; Breccia, A., Cavalleri, B.. Adams, G.E., Eds.; NATO Adv. Study Inst. Ser.; Ser, A.; Plenum Press: New York, 1982; Vol.42, pp 9-34. Boyer, J.H. Nitroimidazoles. In Nitroazoles : The C-nitro derivatives of five-membered N and N,O heterocycles; Henry, F., Ed.; VCH Publishers : Deerfield Beach, FL, 1986; Chapter 2, pp 79-185. Grimmett, M.R. Imidazoles and their benzo derivatives. In Comprehensive Heterocyclic Chemistry. The structure, reactions, synthesis, and uses of heterocyclic compounds; Potts, K.T., Ed.; Katritzky, A.R., Chairman of Ed. Board; Pergamon Press: England, 1984, Vol.5, pp 345-456.

8. Ellis, G.P.; Epstein, C.; Fitzmaurice, C.; Gelberg, L.; Lord, G.H. J.Pharm.Pharmacol. 1964, 16, 801. Cox, J.S.G.; Fitzmaurice, C.; Katritzky, A.R.; Tiddy, G.J.T.; J.Chem.Soc. 1967, 1251.
9. Albright, J.D.; Moran, D.B. J.Heterocycl.Chem. 23, 913 (1986).
10. Searcey, M.; Lee, J.B.; Pye, P.L. Chem.Ind. 1989, 569.
11. Searcey, M.; Lee, J.B.; Pye, P.L. Synth.Commun. 1989, 19(7&8), 1309.
12. Rao, A.K.S.B.; Prasad, R.S.; Rao, C.G.; Singh, B.B. J.Chem.Soc. Perkin Trans.1, 1989, 1352.

13. Rao, A.K.S.B.; Rao, C.G.; Singh, B.B. J.Org.Chem. 1990, 55(11), 3702.

(Received in UK 12 December, 1990)