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

Solid — Liquid Phase — Transfer Catalytic Method for N-Alkylation of Nitroimidazole

Zhen-Zhong Liu [a], Heng-Chang Chen [a], Sheng-Li Cao [a] & Run-Tao Li [a]

[a] Department of Chemistry, Zhengzhou University, Zhengzhou, 450052, People's Republic of China

Published online: 24 Sep 2006.

To cite this article: Zhen-Zhong Liu, Heng-Chang Chen, Sheng-Li Cao & Run-Tao Li (1993) Solid — Liquid Phase — Transfer Catalytic Method for N-Alkylation of Nitroimidazole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:18, 2611-2615, DOI: 10.1080/00397919308012596

To link to this article: http://dx.doi.org/10.1080/00397919308012596

SYNTHETIC COMMUNICATIONS, 23(18), 2611-2615 (1993)

SOLID—LIQUID PHASE—TRANSFER CATALYTIC METHOD FOR N—ALKYLATION OF NITROIMIDAZOLE

Zhen—Zhong Liu* Heng—Chang Chen
Sheng—Li Cao Run—Tao Li

Department of Chemistry, Zhengzhou University,
Zhengzhou 450052, People's Republic of China

ABSTRACT: A variety of 1—alkyl—2—methyl—4—nitroimidazoles have been synthesized with a solid—liquid phase—transfer catalytic method in excellent yield.

Nitroimidazoles are important intermediates for the organic synthesis. Their N—alkyl derivatives have been widely used in the fields of medicine and other fine chemicals. [1,2]

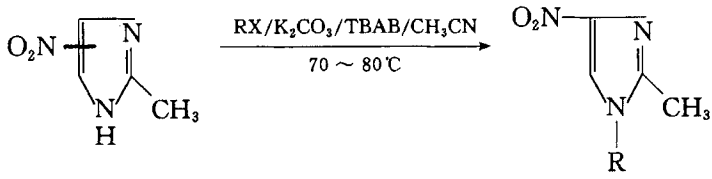
N-alkyl nitroimidazoles usually can be obtained by reacting nitroimidazoles with alkylating agents like alkyl halides or sulfates. The N—alkylation

* To whom correspondence should be addressed.

results in different products according to the reaction conditions. A 1—alkyl—4—nitro derivate is obtained under basic conditions, while the 1—alkyl—5—nitro derivate is the major product under neutral or acidic conditions.[3]. The main methods concerning N—alkylation of nitroimidazoles under basic conditions are as follows. First, in the presence of sodium alcoholate, the reaction is carried out in protic solvents.[4,5,6] Second, the intermediate tetraalkylammonium salts of nitroimidazoles, obtained through reaction of nitroimidazoles with equivalent tetraalkylammonium halide, react with alkyl halides.[7] Third, using tetrabutylammonium bromide as phase—transfer catalyst, the N—alkylation is carried out in the two phase system of aqueous potassium hydroxide and benzene.[7] In the recent literature,[8] A. K. S. B. Rao et al. reported the method that involves reaction of 2—methyl—4(5)—nitroimidazole with alkyl halides in K_2CO_3/DMF at 110 — 120℃. The shortcomings of first three methods are low yield, long reaction time and undesired by—products . Although the yields have been raised and the reaction time shortened with the final method[8], the expensive solvent DMF must be used, and furthermore, the high reaction temperature is not favourable when alkyl halides with low boiling point are used.

In consideration of the high activity of imino—hydrogen, phase—transfer catalysis promises to be a potentially good method for the nucleophilic substitution reaction of nitroimidazoles. However, some loss of halides and occurence of other side reactions can not be avoided due to the contact with aqueous alkali in the liquid—liquid phase—transfer system. In order to eliminate this, we utilized solid—liquid phase—transfer system, in which potassium carbonate was used as alkali, acetonitrile or ethyl acetate as solvent and tetrabutylammonium bromide(TBAB) as catalyst. With this method, a variety of 1—alkyl—2—methyl—4—nitroimidazoles have been synthesized by reacting 2—methyl—4(5)—nitroimidazole with alkyl halides, and the results listed in table 1 show that this method possesses the advantages such as excellent yields, short reaction time and simple operation. The structure of all products were confirmed with elementary analysis, ^{1}H—NMR and IR (Table 2).

TABLE 1



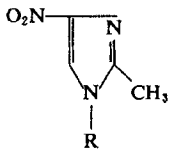
No.	Alkylating agent RX	Reaction time h	Yield %
1	$C_6H_5CH_2Cl$	1	95
2	n—C_4H_9Br	1.5	93
3	n—C_3H_7Br	1.5	95
4	C_2H_5Br	1	84
5	$ClCH_2CH_2OH$*	2	94
6	$C_6H_5CH=CHCH_2Cl$	1.5	86
7	$CH_2=CHCH_2Cl$	3	90
8	n—$C_6H_{13}Br$	2	95
9	$C_6H_5OCH_2CH_2CH_2Br$	1.5	93
10	$ClCH_2COOC_2H_5$	0.5	91

* Using excess 2—chloroethanol as solvent.

EXPERIMENTAL

Melting points were determined on the microscope melting point apparatus and are uncorrected. IR spectra were obtained with a IR—435 infrared spectrophotometer as KBr disks. ^1H—NMR spectra were recorded on a Ac—80 spectrometer using TMS as internal standard, $CDCl_3$ as solvent. Elementary analysis were carried out using a PE2400 element analyzer.

TABLE 2



R	m. p. (℃) (Lit.)	Analysis (%) calcd. (Found) C	H	N	^{1}H—NMR(δ)	IR(cm^{-1})
$CH_2C_6H_5$	106—107 (104—106)[8]	60.83 (61.13)	5.07 (5.19)	19.35 (19.35)	2.40(s,3H, CH_3); 5.12(s,2H,N—CH_2); 7.29(m,5H,Ph); 7.67(s,1H,C_5—H).	3098 1557 1534 1496 1459 1397 1337 1292 833 759 732 702
n—C_4H_9	58—59	52.46 (52.80)	7.10 (7.26)	22.95 (23.10)	0.99(t,3H,CH_3); 1.63(m,4H,CH_2CH_2); 2.44(s,3H,C_2—CH_3) 3.94(t,2H,N—CH_2); 7.71(s,1H,C_5—H).	3121 2963 2938 2868 1537 1499 1380 1331 1293 829 759
n—C_3H_7	55—56	49.70 (50.0)	6.51 (6.64)	24.85 (24.96)	1.0(t,3H,CH_3); 1.81(m,2H,CH_2); 2.44(s,3H,C_2—CH_3) 3.91(t,2H,N—CH_2); 7.71(s,1H,C_5—H).	3111 2970 2936 1532 1503 1402 1326 1293 834 758
C_2H_5	84—86	46.45 (46.24)	5.81 (5.83)	27.10 (27.23)	1.49(t,3H,CH_3); 2.45(s,3H,C_2—CH_3); 3.96(q,2H,N—CH_2); 7.75(s,1H,C_5—H).	3110 1534 1500 1401 1336 1294 1260 1151 993 837 758 683
CH_2CH_2OH	130—131 (129—130)[3]	42.11 (42.62)	5.26 (5.46)	24.56. (24.83)	2.44(s,3H,C_2—CH_3); 4.04(s,4H,CH_2CH_2) 7.73(s,1H,C_5—H).	3306 3145 2950 2930 1542 1500 1415 1331 830 757
CH_2CH=CHC_6H_5	100—102	64.20 (64.63)	5.38 (5.46)	17.28 (17.09)	2.47(s,3H,C_2—CH_3); 4.46(d,2H,N—CH_2); 6.37(m,2H,CH=CH); 7.35(m,5H,Ph); 7.75(s,1H,C_5—H).	3103 1560 1534 1497 1458 1398 1331 1293 833 765 734 693
CH_2CH=CH_2	71—73	50.30 (50.83)	5.39 (5.57)	25.15 (25.26)	2.42(s,3H,C_2—CH_3); 4.55(d,2H,N—CH_2); 5.32(m,2H,=CH_2); 5.87(m,1H,HC=); 7.72(s,1H,C_5—H).	3110 1640 1525 1500 1390 1320 1285 830 755
n—C_6H_{13}	31—33	56.87 (56.90)	8.06 (8.23)	19.91 (20.19)	0.90(t,3H,CH_3); 1.63(m,8H,$(CH_2)_4$); 2.44(s,3H,C_2—CH_3); 3.92(t,2H,N—CH_2); 7.69(s,1H,C_5—H)	3120 2950 1535 1495 1395 1335 1290 825 750
$CH_2(CH_2)_2OC_6H_5$	93—95	59.77 (59.93)	5.75 (6.05)	16.09 (16.32)	2.33(m,2H,CH_2); 2.41(s,3H,C_2—CH_3); 3.97(t,2H,N—CH_2); 4.18(t,2H,CH_2O); 7.06(m,5H,Ph); 7.71(s,1H,C_5—H).	3100 1600 1580 1530 1495 1390 1330 1295 1240 830 745 685
$CH_2COOC_2H_5$	110—112 (111—112)[4]	45.07 (45.28)	5.16 (5.33)	19.72 (19.83)	1.32(t,3H,CH_3); 2.41(s,3H,C_2—CH_3); 4.25(q,2H,OCH_2); 4.70(s,2H,N—CH_2); 7.74(s,1H,C_5—H).	3150 2970 2940 1730 1540 1510 1490 1430 1295 1250 1130 830 755

Typical procedure:

Ethyl 2—methyl—4—nitroimidazole—1—acetate

A mixture of 2—methyl—4(5)—nitroimidazole (2.0g, 15.7mmol), ethyl chloroacetate (2.3g, 18.8mmol), potassium carbonate (4.3g, 31.4 mmol), TBAB (0.1g, 0.31mmol) and acetonitrile (12mL) was stirred vigorously at 70—80℃ for 0.5h. Thin—layer chromatography (silica gel GF_{254} plates) with ethyl acetate as developing agent showed one spot under 254nm uv lamp irradition. After cooling to room temperature, the inorganic salts were filtered off and washed with acetonitrile. The combined acetonitrile solution was evaporated and the residue was recrystallized from ethyl acetate—hexane (2 : 1) to give 3.0g (91%) of ethyl 2—methyl—4—nitroimidazole—1—acetate as white crystal.

REFERENCES

1. Rao, A. K. S. B. ; Rao, C. G. ; Singh, B. B. J. Org. Chem. 1990, 55(11), 3702
2. Johannes, M. ; Resemarie, O. ; Steffen, S. Ger. (East) DD260062, 1988
3. Butler, K. ; Howes, H. L. ; Lynch, J. E. ; Pirie, D. K. J. Med. Chem. 1967, 10, 891
4. Kajfez, F. ; Sunjic, V. ; Kolbah, D. ; Fajdiga, T. ; Oklobdzija, M. J. Med. Chem. 1968, 11, 167
5. Cox, J. S. G. ; Fitzmaurice, C. ; Katritzky, A. R. ; Tiddy, G. J. T. J. Chem. Soc. 1967, 1251
6. Kochergin, P. M. ; Tsygannova, A. M. ; Blinova, L. S. ; Shlikhunova, V. S. Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR 1965(6), 875
7. Searcey, M. ; Pye, P. L. ; Lee, J. B. Synth. Commun. 1989, 19(7&8), 1309
8. Rao, A. K. S. B. ; Rao, C. G. ; Singh, B. B. Synth. Commun. 1991, 21 (3), 427

(Received in the USA 14 April 1993)