SHORT PAPER

J. Chem. Research (S), 2001, 292–293

N-alkylation of amines under microwave irradiation: modified Eschweiler–Clarke reaction†

Séverine Torchy and Didier Barbry*

Laboratoire d'Ingénierie Moléculaire, UPRES 2699, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France

The *N*-alkylation of hexahydroazepine and benzylamine is performed under microwave irradiation in the presence of formic acid and different aldehydes or ketones. Good yields were obtained with reactive carbonyl compounds.

Keywords: *N*-alkylation of amines

The *N*-alkylation of amines is an important reaction in organic synthesis. Alkylation with alkyl halides is the most conventional method[1] but it generates salts as by-products and often exhibits low chemical selectivity. Other reagents such as diazomethane, dialkylcopperlithium or dialkylphosphites have been used for the same purpose but they are dangerous to handle or lead to purification problems.

The reductive amination procedure is also a suitable method for *N*-alkylation using carbonyl compounds. Several reducing agents have been used among which are hydrogen and sodium borohydride with titanium isopropoxide.

Recently, DiMare[2] reported reductive amination using methanolic pyridine-borane and 4 Å molecular sieves. The reaction is performed at room temperature for 3–16 hours. Bogdal[3] developed a general method of *N*-alkylation of heterocycles possessing an acidic hydrogen in 'dry' media under microwave irradiation.

In a previous report,[4] we have prepared tertiary *N*-methyl or *N,N*-dimethyl amines under microwave irradiation in good yields. We noticed that the reaction was easier with secondary amines : indeed they are more nucleophilic and undergo only one methylation. On the other hand, the reaction was more difficult with primary amines : amide formation was a competitive reaction.

We report here the modified Eschweiler–Clarke reaction under microwave irradiation : we have first reproduced previous results[4] (in a domestic oven) obtained in the presence of paraformaldehyde in a monomode oven (Synthewave 402). A 70 % yield of *N*-methylhexahydroazepine was obtained after 4 min of irradiation at low power (30 W) with 2.5 equivalents of both paraformaldehyde and formic acid.

Next, we tried to extend this method to other aldehydes and ketones. The carbonyl group should influence the yield of the reaction: indeed, carbonyl group compounds in which α-hydrogen atoms are present can lead in acid medium, to products of aldol reaction. However, a 63 % yield of *N,N*-dibutylpiperazine was obtained[5] upon refluxing butyraldehyde with piperazine in formic acid for three hours.

The results are summarized in Table 1. In some cases, we have observed amide formation (*N*-formylhexahydroazepine). Aliphatic aldehydes are so reactive that the *N*-alkylation occured twice times to prevent aldol condensation.

We then studied one case of a primary amine, benzylamine. We have noticed the presence of amide (*N*-formylbenzylamine), and in some cases the formation of monoalkylated products. The results are summarised in Table 2. In the case of benzaldehyde, we observed the presence of a the dibenzylformamide, formed from the monosubstituted amine. We have noticed with cyclopentanone the presence of imine which was not reduced by formic acid; a longer irradiation time might

Table 2 *N*-alkylation of benzylamine under microwave irradiation (30 W), 4 equiv HCOOH, 5 min

Carbonyl compound	Equivalents of carbonyl compound	Amine	Amide
Paraformaldéhyde	2.5	66 % **	–
Benzaldehyde	2.5	59 % **	40 % **
o-CF_3PhCHO	2.5	<5 % **	6 %*
Cyclopentanone	2.5	39 % * (+ 9 % imine)	14 %*
Cyclohexanone	2.5	62 % *	4 %*
Cycloheptanone	2.5	12 % *	4 %*
Hexanal	1.5	10 %*	–
Heptanal	2.5	10 % *	–
Pentan-2-one	2.5	–	–

**N*-alkyl compound; ** *N,N*-dialkyl compound.

Table 1 *N*-alkylation of hexahydroazepine under microwave irradiation (30 W), 2.5 equiv HCOOH

Carbonyl compound	Equivalents of carbonyl compound	Time	*N*-alkylated amine	Amide
Paraformaldehyde	2.5	4 min	70 %	–
Benzaldehyde	2.5	4 min	66 %	–
o-CF_3PhCHO	1.5	4 min	66 %	–
Cyclopentanone	1.5	4 min	75 %	11 %
Cyclohexanone	1.5	4 min	53 %	10 %
Cycloheptanone	1.5	4 min	28 %	49 %
Hexanal	1.2	2 min 30 + 3 min	74 %	10 %
Heptanal	1.5	2 min 30 + 3 min	81 %	–
Pentan-3-one	1.5	4 min	–	4 %
Pentan-2-one	1.5	4 min	–	–

* To receive any correspondence. E-mail: Didier.Barbry@univ-lillel.fr

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

resolve this problem. The monomethylation of benzylamine can be explained by steric hindrance.

In conclusion, we have developed a one-pot *N*-alkylation of amines using formic acid under microwave irradiation. Our method is extremely fast and simple. However, this results show that this process must be used with reactive carbonyl compounds.

Experimental

NMR spectra were recorded on a Bruker AC 300 spectrometer in deuterochloroform. Microwave assisted organic reactions were performed in a Synthewave 402 oven in an open vessel. Mass spectra were recorded on a MALDI-TOF Vision 2000, FINNIGAN MAT spectrometer. All of the known products were characterised with comparison of their NMR spectra with those of the literature.

General procedure: A mixture of amine (10 mmol), formic acid (25–40 mmol) and carbonyl compound (15–25 mmol) was irradiated in a microwave oven (30 W). The reaction mixture was allowed to cool and diluted with water (5 ml) and ether (10 ml). The solution was acidified with a 6 N solution of hydrochloric acid. The organic layer was separated to remove amide if present, the ether extract was dried over magnesium sulfate and concentrated. Potassium hydroxide potassium was added to the aqueous layer and alkylated amine was then extracted thrice with ether (10 ml). The organic layers were dried over potassium carbonate and concentrated. Crude products were analysed by NMR.

N- formylhexahydroazepine[6]*:* ^{1}H NMR: 1.5–1.9 (m, 8H), 3.4–3.6 (m, 4H), 8.12 (s, 1H) ; ^{13}C NMR : 26.8 (CH_2), 26.9 (CH_2), 27.9 (CH_2), 30.2 (CH_2), 43.5 (CH_2), 47.7 (CH_2), 162.8 (CHO).

N-methylhexahydroazepine[7]*:* ^{1}H NMR : 1.26–1.46 (m, 8H), 2.08 (s, 3H), 2.30 (t, 4H); ^{13}C NMR : 26.4 (CH_2), 27.7 (CH_2), 47.1 (CH_3), 58.2 (CH_2).

N-benzylhexahydroazepine[8]: ^{1}H NMR: 1.62 (m, 8 H), 2.62 (m, 4 H), 3.64 (s, 2H), 7.2–7.4 (m, 5 H); ^{13}C NMR : 27.0 (CH_2), 28.1 (CH_2), 55.6 (CH_2), 62.7 (CH_2), 126.7 (CH), 128.0 (CH), 128.8 (CH), 139.9 (C).

N-(o-trifluromethylbenzyl)hexahydroazepine: ^{1}H NMR : 1.55–1.61 (m, 8 H), 2.59-2.61 (m, 4 H), 3.76 (s, 2 H), 7.25 (t, 1 H), 7.48 (t, 1 H), 7.56–7.58 (d, 1 H, J = 7.8 Hz), 7.87–7.89 (d, 1 H); ^{13}C NMR: 26.9 (CH_2), 28.5 (CH_2), 55.9 (CH_2), 58.3(CH_2), 125.4 (CF_3), 126.3 (C), 130.0 (CH), 131.6 (CH), 139.7 (C); Found: C, 65.22; H, 7.11; N, 5.41%. $C_{13}H_{16}NF_3$ requires: C, 65.35; H, 7.05; N, 5.44%. Hydrochloride : m/z = 258.3 (positive ion) ; m.p. = 130°C.

N-cyclopentylhexahydroazepine[9]: ^{1}H NMR: 1.30–1.88 (m, 16 H), 2.58–2.61 (m, 4 H), 2.76–2.87 (m, 1 H); ^{13}C NMR: 24.2 (CH_2), 26.9 (CH_2), 28.0 (CH_2), 30.3 (CH_2), 53.7 (CH_2), 66.0 (CH).

N-cyclohexylhexahydroazepine[10]*:* ^{1}H NMR : 1.10–1.30 (m, 4 H), 1.40–1.55 and 1.60–1.80 (m, 12 H), 2.30–2.45 (m, 1 H), 2.60 (t, 4 H); ^{13}C NMR: 26.1 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 29.1 (CH_2), 51.5 (CH_2), 64.2 (CH).

N-cycloheptylhexahydroazepine[11]: ^{1}H NMR : 1.39–1.72 (m, 20 H), 2.39–2.50 (m, 5 H); ^{13}C NMR: 24.3 (CH_2), 26.0 (CH_2), 26.7 (CH_2), 29.7 (CH_2), 43.8 (CH_2), 51.8 (CH_2), 66.8 (CH).

N-hexylhexahydroazepine[12]*:* ^{1}H NMR : 0.82 (t, 3 H), 1.16-1.25 (m, 6 H), 1.37–1.41 (m, 12 H), 1.50–1.53 (m, 8 H), 2.53–2.56 (t, 4 H); ^{13}C NMR: 14.0 (CH_3), 22.8 (CH_2), 26.8 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 27.7 (CH_2), 31.8 (CH_2), 55.5 (CH_2), 58.4 (CH_2).

N-heptylhexahydroazepine[13]: ^{1}H NMR : 0.84 (t, 3 H), 1.35–1.71 (m, 18 H), 2.37–2.42 (t, 2 H), 2.56–2.59 (t, 4 H); ^{13}C NMR: 14.1 (CH_3), 22.6 (CH_2), 27.0 (CH_2), 27.6 (CH_2), 27.7 (CH_2), 27.9 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 55.6 (CH_2), 58.5 (CH_2).

N-benzylformamide[14]*:* ^{1}H NMR : 4.40 (d, 2 H), 6.75 (s, 1 H), 7.15–7.40 (m, 5H), 8.12 (s, 1 H); ^{13}C NMR: 41.8 (CH_2), 127.4 (CH), 127.6 (CH), 128.5 (CH), 137.5 (C), 161.2 (CHO).

N,N-dimethylbenzylamine[15]*:* ^{1}H NMR : 2.20 (t, 6 H), 3.60 (s, 2 H), 7.3 (m, 5 H); ^{13}C NMR : 45.5 (CH_3), 64.4 (CH_2), 127.0 (CH), 128.2 (CH), 129.1 (CH), 138.9 (C).

N,N,N-tribenzylbenzylamine[16]*:* ^{1}H NMR : 3.55 (s, 6 H), 7.19–7.42 (m, 15 H) ^{13}C NMR: 57.9 (CH_2), 126.8 (CH), 128.2 (CH), 128.7 (CH), 139.6 (C).

N-hexylbenzylamine[17]*:* ^{1}H NMR: 0.85 (t, 3 H), 1.20–1.50 (m, 8 H), 1.90 (s, 1 H), 2.59 (t, 2 H), 3.80 (s, 2 H), 7.15–7.35 (m, 5 H); ^{13}C NMR: 14.1 (CH_3), 22.6 (CH_2), 27.1 (CH_2), 30.1 (CH_2), 31.8 (CH_2), 49.5 (CH_2), 54.1 (CH_2), 126.6 (CH), 127.8 (CH), 128.3 (CH), 140.3 (C).

N- heptylbenzylamine[18]: ^{1}H NMR : 0.95 (t, 3 H), 1.20–1.50 (m, 10 H), 2.1 (s, 1 H), 2.55 (t, 2 H), 3.81 (s,2 H), 7.20–7.33 (m, 5 H); ^{13}C NMR: 14.1 (CH_3), 23.7 (CH_2), 27.1 (CH_2), 30.1 (CH_2), 31.8 (CH_2), 49.5 (CH_2), 54.1 (CH_2), 126.8 (CH), 128.1 (CH), 128.3 (CH), 140.0 (C).

N-cyclopentylbenzylamine[19]: ^{1}H NMR : 1.25–1.10 (m, 2 H), 1.45–1.58 (m, 2 H), 1.60–1.84 (m, 4 H), 3.04–3.09 (m, 1 H), 3.71 (s, 2 H), 4.37 (s, 1 H), 7.17–7.28 (m, 5 H) ; ^{13}C NMR : 24.0 (CH_2), 33.1 (CH_2), 52.7 (CH_2), 59.1 (CH), 126.8 (CH), 128.1 (CH), 128.3 (CH), 140.5 (C).

N-cyclohexylbenzylamine[20]*:* ^{1}H NMR: 1.01–1.30 (m, 6H), 1.60–1.91 (m, 5 H), 2.40–2.51 (m, 1 H), 3.78 (s, 2 H), 7.17–7.30 (m, 5 H); ^{13}C NMR: 24.8 (CH_2), 26.0 (CH_2), 33.3 (CH_2), 50.8 (CH_2), 55.9 (CH), 126.5 (CH), 127.8 (CH), 128.1 (CH), 140.8 (C).

N-cycloheptylbenzylamine: ^{1}H NMR: 1.36–1.55 (m, 8 H), 1.60–1.90 (m, 5 H), 2.64–2.67 (m, 1 H), 3.74 (s, 2 H), 7.21–7.32 (m, 5 H); ^{13}C NMR: 24.3 (CH_2), 28.3 (CH_2), 34.7 (CH_2), 51.5 (CH), 58.3 (CH_2), 126.8 (CH), 128.1 (CH), 128.3 (CH), 140.7 (C); Found : C, 81.83; H, 10.30%. $C_{14}H_{21}N$ requires: C, 82.70; H, 10.41%. Hydrochloride: m/z = 204.4 ; m.p. = 262°C.

N,N-dibenzylformamide[21]*:* ^{1}H NMR: 4.24 (s, 2H), 4.37 (s, 2H), 7.10–7.45 (m, 10H), 8.41 (s, 1H); ^{13}C NMR: 44.6 (CH_2), 50.2 (CH_2), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 135.1 (C), 135.4 (C), 162.9 (CHO).

Received 30 December 2000; accepted 27 February 2001
Paper 00/682

References

1 K. Mohri, K. Suzuki, M. Usui, K. Isobe and Y. Tsuda, *Chem. Pharm. Bull*., 1995, **43**, 159.
2 M.D. Bomann, I.C. Guch and M. DiMare, *J. Org. Chem*., 1995, **60**, 5995.
3 D. Bogdal, J. Pielichowski and K. Jaskot, *Heterocyles*, 1997, **45**, 715.
4 D. Barbry and S. Torchy, *Synth. Comm*.,1996, **26**, 3919.
5 W.T. Forsee and C.B. Pollard, *J. Am. Chem. Soc*., 1935, **57**, 1788.
6 K. Ogawa, Y. Nomura, Y. Takeuchi and S. Tomoda, *J. Chem Soc. Perkin Trans. 1*, 1982, **12**, 3031.
7 R. Lukes and J. Malek, *Chem.Listy*, 1951, **45**, 72.
8 Z. Zhang and I. Ojima, *J. Organomet. Chem*., 1993, 281.
9 A.F. Abdel-Magid, K.G. Carson, B.D. Harris, C.A. Maryanoff and R.D. Shah, *J. Org. Chem*., 1996, **61**, 3849.
10 S.C. Shim, C.H. Doh, T.J. Kim, H.K. Lee and K.D. Kim, *J. Heterocycl. Chem*., 1988, **25**, 1383.
11 A.G. Cook, M.L. Absi and V.K. Bowden, *J. Org. Chem*., 1995, **60**, 3169.
12 S.H. Murahashi, K. Kondo and T. Hakata, *Tetrahedron Lett*., 1982, **23**, 229.
13 F.Y. Rachinskii, T.G. Potapenko, O.D. Shapilov, V.T. Osipyan and A.A. Krupenina, *Zh. Prikl. Khim*., 1968, **41**, 1072; *Chem. Abstr. 1968*, **69**, 106532q.
14 A.R. Katritzky, H.X. Chang and B. Yang, *Synthesis*, 1995, 503.
15 S.H. Pine and B.L. Sanchez, *J. Org. Chem*., 1971, **36**, 829.
16 A.R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala and L. Urogdi, *J. Chem. Soc. Perkin Trans. 1*, 1989, 225.
17 A.R. Katritzky and M. Drewniak, *J. Chem. Soc. Perkin Trans. 1*, 1988, 2339.
18 H. King and T.S. Work, *J. Chem. Soc*., 1940, 1307; *Chem. Abstr.* 1941, **35**, 115[6].
19 W.R. Bowmann, P.T. Stephenson, N.K. Terrett and A.R. Young, *Tetrahedron*, 1995, **51**, 7959.
20 M.B. Sassaman, *Tetrahedron*, 1996, **52**, 10835.
21C. Bovel, L.S. Hegedus, J. Krebs and Y. Satch, *J. Am. Chem. Soc*. 1987, **109**, 1101.