Effect of Ultrasound on One-Pot Conversion of Alcohols to Nitro and Azido Compounds

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Synthesis of aliphatic nitro and azido compounds from corresponding alcohols under ultrasonic irradiation was studied. Ultrasonic irradiation of the reaction mixture $ROH/NaNO_2/HCl$ allowed to shorten the reaction time and increase yields of aliphatic nitro compounds. Ultrasonic irradiation of the reaction mixture $PhCH_2OH/NaN_3/PPh_3$ resulted in formation of $PhCH_2N_3$ in yields comparable with those of the silent experiments. The next product was benzyl chloride and not benzylamine as was described in the literature.

Aliphatic nitro compounds are valuable intermediates in organic synthesis [1-4] and organic chemists devote a great attention to their preparation. Very frequent method for preparation of aliphatic nitro compounds is oxidation of primary amines with potassium permanganate [5]. Barnes and Patterson prepared aliphatic nitro compounds from chlorinated ketoximes by ozonolysis followed by catalytic hydrogenation [6]. Nitration of saturated hydrocarbons with nitric acid was carried out under rather harsh conditions $(250-400^{\circ}C)$, which resulted in the cleavage of C-H and C-C bonds worsening thus selectivity [7]. Catalytic nitration of saturated alkanes using nitric acid under mild conditions was described recently [8]. N-Hydroxyphthalimide was used as the catalyst and the key step of this method was in situ generation of NO_2 and phthalimide *N*-oxyl radical. Aliphatic nitro compounds are often prepared from carbenoids [9], carboxylic acid [10], etc. Baruah [11] described a simple and efficient one-pot synthesis of aliphatic nitro compounds from corresponding alcohols and NaNO₂/CH₃COOH/HCl/CH₂Cl₂ reaction system in 70-92 % yields.

Azides are usually prepared by conversion of alcohols to halides or sulfonates followed by nucleophilic substitution with azide anion [12] or by conversion of alcohols in a Mitsunobu reaction [13]. Reddy et al. [14] described an efficient synthesis of azides and amines from alcohols using sodium azide and triphenylphosphine in the CCl₄—DMF solvent system. Treatment of alcohols with sodium azide and one equivalent of PPh₃ resulted in azides, treatment of alcohols under the same conditions with two equivalents of PPh₃ afforded corresponding amines.

EXPERIMENTAL

Chemical reagents and solvents were commercially available and purified (distilled and chromatographed, respectively) before application in reactions. All products were analyzed by ¹H NMR and GC-MS spectroscopy. The ¹H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in CDCl₃ with tetramethylsilane as an internal standard. Melting points were determined on a Koffler hot-stage apparatus. GC analyses were recorded on a GC Trace 2000 Series instrument, mass spectra were recorded on a Voyager spectrometer. All sonochemical experiments were carried out in a glass reactor fitted to an ultrasonic horn ULTRAGEN (20 kHz, 300 W) under pulsed conditions (pulse length: 4 s, 50 % duty) or in an ultrasonic cleaning bath (20 kHz) under air.

Preparation of Aliphatic Nitro Compounds from Alcohols

To a solution of alcohol (0.009 mol) in CH₂Cl₂ (30 cm³) NaNO₂ (2 g; 0.029 mol) and acetic acid (1.5 cm³) were added. This mixture was left for 5 min at room temperature and then concentrated HCl (0.5 cm³) was added. The reaction mixture was irradiated for time shown in Tables 1—3 under external cooling in an ice bath. Temperature of the reaction mixture attained 25 °C at the end of sonication. In classical experiment the reaction mixture was left at room temperature without stirring for the time given in Tables 1—3.

The reaction mixture was then diluted with CH_2Cl_2 (150 cm³) and the precipitated sodium acetate was filtered off. The organic phase was evaporated *in vacuo*,

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the residue was dissolved in isohexane (100 cm³) and washed with water (3 × 200 cm³). The organic phase was dried over anhydrous sodium sulfate. Solvent was evaporated *in vacuo* and the residue analyzed by ¹H NMR spectroscopy. Products were isolated by column chromatography on SiO₂ using isohexane—ethyl acetate ($\varphi_r = 10:1$) as the eluent.

(*Nitromethyl*)benzene (IIa). ¹H NMR spectrum, δ : 5.70 (s, 2H, CH₂), 7.33—7.36 (m, 5H, H_{arom}). ¹H NMR data are consistent with literature [11]. MS, m/z: 107 (M - NO), 91 (M - NO₂), 77 (C₆H₅); for C₇H₇NO₂ calc. $M_{\rm r} = 137$.

1-Bromo-4-(nitromethyl)benzene (IIb). ¹H NMR spectrum, δ : 5.65 (s, 2H, CH₂), 7.23 (d, 2H, H_{arom}), 7.51 (d, 2H, H_{arom}). MS, m/z: 186 (M – NO), 156 (M – CH₂NO₂), 77 (C₆H₅); for C₇H₆BrNO₂ calc. $M_{\rm r}$ = 216.

 $\begin{array}{l} 1-(Phenylsulfanyl)-4-(nitromethyl)benzene \ (IIc).\\ {}^{1}\mathrm{H} \ \mathrm{NMR} \ \mathrm{spectrum}, \ \delta: \ 5.64 \ (\mathrm{s}, \ 2\mathrm{H}, \ \mathrm{CH}_{2}), \ 7.21\mbox{--}7.37 \\ (\mathrm{m}, \ 9\mathrm{H}, \ \mathrm{H}_{\mathrm{arom}}). \ \mathrm{MS}, \ m/z: \ 215 \ (\mathrm{M} - \mathrm{NO}), \ 155 \ (\mathrm{M} - \mathrm{CH}_{2}\mathrm{NO}_{2}), \ 77 \ (\mathrm{C}_{6}\mathrm{H}_{5}); \ \mathrm{for} \ \mathrm{C}_{13}\mathrm{H}_{11}\mathrm{NO}_{2}\mathrm{S} \ \mathrm{calc.} \ M_{\mathrm{r}} = \end{array}$

245. 1-Nitropentane (VId). ¹H NMR spectrum, δ : 0.90 (t, 3H, CH₃), 1.23—1.25 (m, 4H, 2 × CH₂), 1.58— 1.61 (m, 2H, CH₂), 3.62 (t, 2H, CH₂NO₂). ¹H NMR data are consistent with literature [15].

2-Nitrohexane (VIe). ¹H NMR spectrum, δ : 0.92 (t, 3H, CH₃), 1.28 (d, 3H, CH₃), 1.54—1.59 (m, 6H, 3 × CH₂), 4.06—4.17 (m, 1H, CH). ¹H NMR data are consistent with literature [15].

2-Nitrooctane (VIf). ¹H NMR spectrum, δ : 0.88 (t, 3H, CH₃), 1.34 (d, 3H, CH₃), 1.54—1.73 (m, 10H, 5 × CH₂), 4.09—4.16 (m, 1H, CH). ¹H NMR data are consistent with literature [15].

Preparation of Benzyl Azide from Benzyl Alcohol

A mixture of benzyl alcohol $(0.52 \text{ cm}^3; 0.005 \text{ mol})$, sodium azide (0.325 g; 0.005 mol or 0.650 g; 0.010 mol), and triphenylphosphine (1.3 g; 0.005 mol or 2.6 mol) g; 0.010 mol) in CCl₄—DMF ($\varphi_r = 1:4$) (20 cm³) was irradiated for time shown in Table 4. Temperature of the reaction mixture attained 93—95 °C at the end of sonication. In classical experiment the reaction mixture was heated at 90 °C with stirring for 1 h.

The reaction mixture was then brought to room temperature, poured into water (150 cm³) and the emulsion formed was extracted into diethyl ether (3 × 100 cm³). The ethereal solution was filtered through SiO₂ column under reduced pressure to remove triphenylphosphine oxide. Organic solution was dried over anhydrous sodium sulfate, ether was evaporated and the crude product was analyzed by ¹H NMR spectroscopy.

Benzyl azide (VII). ¹H NMR spectrum, δ : 4.34 (s, 2H, CH₂), 7.26—7.45 (m, 5H, H_{arom}). ¹H NMR data are consistent with literature [16].

RESULTS AND DISCUSSION

Conversion of alcohols to corresponding nitro compounds using NaNO₂/CH₃COOH/HCl/CH₂Cl₂ is a heterogeneous process, therefore we tried to improve it by application of ultrasonic irradiation. To start the study, a classical reaction was performed and the results were compared with those described in the literature. *Baruah* [11] described an 85 % yield of (nitromethyl)benzene (*Ha*) obtained in classical reaction, but we obtained at his conditions just 34 % of *Ha* after 14 h (Scheme 1, Table 1). Ultrasonic irradiation markedly improved yields of *Ha*. After 15 min of sonochemical reaction we obtained *Ha* in 42—64 % yields.

Since preparation of aliphatic nitro compounds described in literature [11] suffered from a poor atom economy, it was interesting whether excess of NaNO₂ (Ia—NaNO₂ mole ratio 1:3) is necessary. Using Ia— NaNO₂ mole ratio 1:3 in sonochemical reaction, IIawas obtained in 64 % yield. Decreasing of Ia—NaNO₂ mole ratio to 1:2 reduced the yield of IIa to 50 % and further lowering of the mole ratio to 1:1 reduced the yield to 42 %. Increasing of the molar excess of

Run	Ia—NaNO ₂ mole ratio	Reaction	Time	Conversion of Ia	Yield of IIa
			min	%	%
1	1:3	Silent	14 h	81	$34 (85^a)$
2	1:1))))	15	58	42
3	1:2))))	15	62	50
4	1:3))))	15	68	64
5	1:4))))	15	50	51
6	1:5))))	15	43	43
7	1:3))))	30	70	65
8	1:3))))	60	53	40^{b}
9	1:3))))	60	0	0^c

Table 1. Influence of Reaction Conditions on Synthesis of (Nitromethyl) benzene (IIa) (X = H) from Benzyl Alcohol (Ia)

a) Data from Ref. [11]; b) reaction was performed with 0.092 mol of benzyl alcohol under external cooling, reaction temperature 10° C; c) reaction was performed in an ultrasonic cleaning bath.



NaNO₂ above 3 had similar effect on the reaction course. This observation is probably due to the fact that mixing and mass transfer is less effective, when a great amount of NaNO₂ is present in the reaction mixture. Prolonging of the reaction time from 15 min to 30 min using Ia—NaNO₂ mole ratio 1:3 did not influence the results.

To investigate the synthetic usefulness of this method, an experiment with tenfold excess of the reactant (0.092 mol of Ia) was performed. Sonication for 60 min gave 40 % of IIa isolated by column chromatography.

We assume that the positive effect of ultrasonic irradiation is due to its mechanical effects and effective mass transfer. That is why the reaction in an ultrasonic cleaning bath (in contrast to the ultrasonic horn reactor) gave no product after 60 min of irradiation. Only starting material was detected in the reaction mixture by ¹H NMR spectroscopy.

To check the electron effects on the reaction course, we performed this reaction with different 4-

Table 2. Results of Sonochemical Synthesis of Nitromethyl-
arenes IIa—IId from Alcohols Ia—Id; Reaction Time
15 min; Alcohol—NaNO2 Mole Ratio 1:3

C I	Х	Conversion of I Yield of II Yield of III,		
Compound		%	%	%
Ia	Н	68	64	< 5
1b Ic	$^{\mathrm{Br}}_{\mathrm{PhS}}$	65 60	$\frac{57}{52}$	< 5 < 5
Id	NO_2	3	0	0

substituted benzyl alcohols (Table 2). Bromo and phenylsulfanyl groups had no significant influence on the reaction course. Strong electron-withdrawing nitro group inhibited the reaction. The traces (< 5 %) of corresponding aldehydes (*IIIa—IIId*) and esters (*IVa—IVd*) were detected by ¹H NMR and GC-MS analyses in all studied reactions.

Table 3. Influence of Reaction Conditions on Synthesis of Nitro Alkanes VIa—VIf from Alcohols Va—Vf; Alcohol—NaNO₂ MoleRatio 1:3

a i	R	Reaction	Time	Yield of VIa—VIf	
Compound			min	%	
Va	CH_3CH_2))))	15	0^a	
Vb	$(CH_3)_3C$))))	15	0^a	
Vc	Cyclohexyl))))	15	0^a	
Vd	$CH_3(CH_2)_4$))))	15	50	
Ve	$CH_3[CH_2]_3(CH_3)CH$))))	15	61	
Ve	$CH_3[CH_2]_3(CH_3)CH$	Silent	7 h	38	
V f	$CH_3[CH_2]_5(CH_3)CH$))))	15	69	
Vf	$CH_3[CH_2]_5(CH_3)CH$))))	30	$81 \ (90^b)$	
Vf	$CH_3[CH_2]_5(CH_3)CH$))))	45	$83(95^{b})$	
Vf	$CH_3[CH_2]_5(CH_3)CH$	Silent	7 h	56	

a) Only starting material was detected in the reaction mixture. b) Conversion of Vf.



Ethanol (Va), tert-butanol (Vb), and cyclohexanol (Vc) were inactive in this procedure (Scheme 2, Table 3), but beneficial ultrasound effect was markedly manifested in reactions of hexan-2-ol (Ve) and octan-2-ol (Vf). Silent reactions (7 h) gave 38 % of 2-nitrohexane (VIe) and 56 % of 2-nitrooctane (VIf), while sonochemical reactions (15 min) gave 61 % of VIe and 69 % of VIf. Prolonging of the sonochemical transformation of octan-2-ol (Vf) from 15 to 30 min improved the yields of 2-nitrooctane (VIf) from 69 to 81 %. Further prolongation of the reaction time did not improve the yield.

Having promising results of sonochemical conversions of aliphatic alcohols to corresponding nitro compounds, we decided to study an ultrasound effect on transformation of benzyl alcohol to benzyl azide (VII) and benzyl chloride (VIII), respectively (Scheme 3, Table 4). Reddy [14] described 95 % yield of VII after 1 h reaction of Ia with NaN₃ and PPh₃. We tried to repeat this reaction, but, apart from VII, VIII was detected by ¹H NMR and GC-MS analyses in the reaction mixture, too. Conversion of starting material was 100 % and the VII—VIII mole ratio was 60:40. The same results were obtained at 45 min of sonochemical reaction. To eliminate formation of VIII, this reaction was performed in pure DMF without CCl₄. Silent reaction (60 min) gave no product, only starting material Ia was detected in the reaction mixture. To improve the reaction selectivity, the silent reaction was repeated with two equivalents of NaN₃. Compound VII was the only product, but the conversion of Iadecreased to 50 %. According to the literature [14], reaction of Ia with one equivalent of NaN₃ and two equivalents of PPh₃ gave 96 % of benzylamine. On the contrary, with the same mole ratio of reactants, VIII was the only product of the sonochemical reaction (1 h).

The reproducibility of the sonochemical reactions was very good. The experiments were repeated two or three times with very similar results.

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REFERENCES

- Pham-Huu, D. P., Petrušová, M., BeMillar, J. N., and Petruš, L., *Tetrahedron Lett.* 40, 3053 (1999).
- Tamura, R., Kamimura, A., and Ono, N., Synthesis 1991, 423.
- Kalita, D., Khan, A. T., Saikia, A. K., Bez, G., and Barua, N. C., Synthesis 1998, 975.
- Kalita, D., Khan, A. T., Barua, N. C., and Bez, G., *Tetrahedron* 55, 5177 (1999).
- 5. Emmons, W. D., J. Am. Chem. Soc. 79, 5528 (1957).
- Barnes, M. W. and Patterson, J. M., J. Org. Chem. 41, 733 (1976).
- 7. Bachmann, G. B., J. Org. Chem. 17, 906 (1952).
- Shinji, I., Nishiwaki, Y., Sakaguchi, S., and Ishii, Y., Chem. Commun. 2001, 1352.
- Sitzmann, M. E., Kaplan, L. A., and Angres, I., J. Org. Chem. 42, 1580 (1977).
- Bachmann, G. B. and Biermann, T. F., J. Org. Chem. 35, 4229 (1970).
- Baruah, A., Kalita, B., and Barua, N. C., Synlett 2000, 1064.
- 12. Rolla, F. J., J. Org. Chem. 47, 4327 (1982).
- Loibner, H. and Zbiral, E., *Helv. Chim. Acta* 59, 2100 (1976).

Run	$Ia/NaN_3/PPh_3$ mole ratio	Reaction	Time	Conversion of Ia	w(VII)	w(VIII)
			min	%	%	%
1	1:1:1))))	45	100	60	40
2	1:1:1	Silent	60	100	60	40
3	1:1:1	Silent	60	0^a	_	_
4	1:2:1	Silent	60	50	100	0
5	1:1:2))))	60	100	$0 (96^b)$	100

Table 4. Results of Reaction of Benzyl Alcohol (Ia) with NaN₃/PPh₃

a) Reaction performed without CCl_4 in pure DMF; b) data from Ref. [14], silent reaction, reaction time 4 h.

- Reddy, G. V. S., Rao, G. V., Subramanyam, R. V. K., and Lyengar, D. S., Synth. Commun. 30, 2233 (2000).
 Katritzky, A. R., Kashmiri, M. A., and Wittmann, D.
- Katritzky, A. R., Kashmiri, M. A., and Wittmann, D T., *Tetrahedron 40*, 1501 (1984).
- Alvarez, S. G. and Alvarez, M. T., Synthesis 4, 413 (1997).