A Convenient Method For The Preparation of *gem*-Halonitro Compounds

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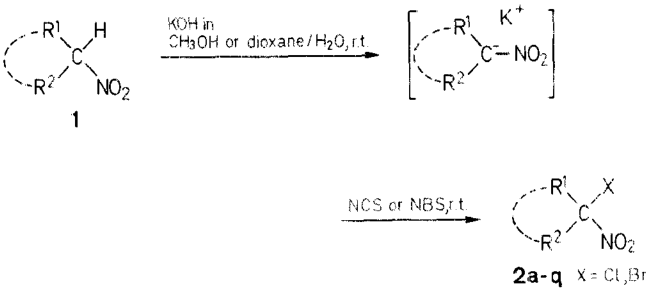
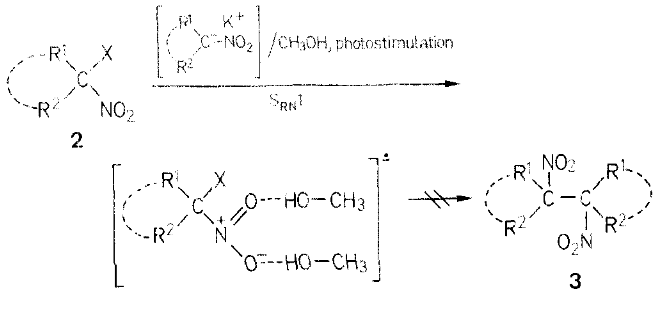
Aliphatic nitro compounds are easily halogenated by *N*-chloro- or *N*-bromosuccinimide in protic solvents to give the practically pure *gem*-halonitro compounds

Treatment of potassium, sodium, or lithium salts of aliphatic nitro compounds with chlorine gas or bromine is the general method for the preparation of *gem*-chloronitro or *gem*-bromonitro compounds[1] which are good substrates for studying $S_{RN}1$(Al) reactions[2]. In the course of our investigations in this field[3], we have used a more efficient and simpler method for the preparation of this type of compounds which we report in the present communication. *N*-chloro- and *N*-bromosuccinimide are known as halogenating agents for oximes[4], sulfoxides[5], and enol borinates[6] and we have observed that in protic medium (methanol or dioxane/water) these reagents react also with the potassium salts of nitro compounds **1** to give the *gem*-halonitro compounds **2**. The reaction is exothermic and fast (15–30 min) and practically pure products are obtained in high yield.



The thus formed *gem*-halonitro compounds **2** could undergo an $S_{RN}1$(Al) reaction in the presence of the potassium salt of the nitro compound **1** to give the $S_{RN}1$ product **3**, but this is not observed here since the radical anion formed in the first step of such a reaction is solvated by the protic solvent whereby its dissociation is strongly retarded[7]. As a consequence, the halogenation reaction is not affected by light, but an inert atmosphere (Argon) is necessary to prevent the autoxidation of the nitronate[8,9].



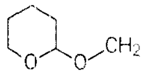
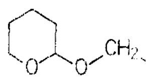
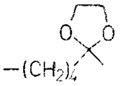
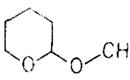
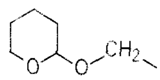
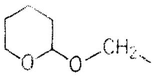
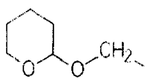
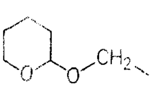
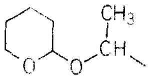
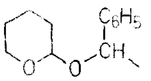
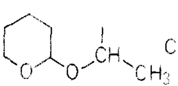
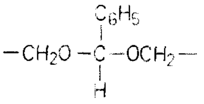
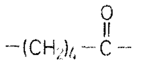
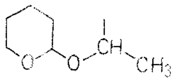
The method is successful when applied to a great variety of nitro compounds, including the polysubstituted compounds **1l, m, n, o** possessing labile protons. The unprotected 2-nitropropanol (**1q**) is easily halogenated, but the method fails for the α-nitro ketone **1r** and gives a poor yield for a molecule such **1s** possessing labile protons adjacent to the nitro function. Methanol is the solvent of choice, but the mixture dioxane/water is also suitable and it has to be used for treating **1d,o** which are sensitive to methanol under basic conditions.

Nitrocyclohexane (Fluka), 2-nitropropanol (Fluka), and 2-bromo-2-nitro-1,3-propanediol (Aldrich) were commercially available. Other nitrocompounds were pepared according to literature procedures: **1c, f** by Michael addition of the corresponding nitroalkane to methyl acrylate[10]; **1m, n, o** by Henry reaction between 4-nitrobutanenitrile or 4-nitromethyl butanoate and benzaldehyde or acetaldehyde using alumina as catalyst[11]. A new procedure described in the next communication[12] led to **1j, p**. Functional-group protection was achieved with dihydropyran (**1g, 1j**) or by acetalization (**1i**[13], **1p**[14]); **1d** was obtained by treatment of ethyl 2-bromopropanoate with sodium nitrite in dimethylformamide[15].

gem-Halonitro Compounds (2); General Procedure:

To a stirred solution of potassium hydroxide (1.123 g, 20 mmol) in methanol (80 ml) or in dioxane/water (70:30; 80 ml) is added a solution of the nitroalkane **1** (20 mmol) in methanol (20 ml) or in

Table 1. Halogenation of Aliphatic Nitro Compounds (**1**) with *N*-Chloro- or *N*-Bromosuccinimide in Alkaline Medium

Product **2**	R^1	R^2	X	Reaction Conditions		Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. Data	MS[c] *m/e*
				Solvent	Time [*min*]				
a	CH_3	CH_3	Cl	methanol	45	95	b.p. 130–132/760	b.p. 131/760	
b	CH_3	CH_3	Br	methanol	30	90	m.p. 33–35[d]		
c	$-(CH_2)_5-$		Cl	methanol	40	~100	b.p. 35–40/0.35[e]	b.p. 81–82/8[16]	163 + 165 (M^+), 117 + 119, 81
d	CH_3	$COOC_2H_5$	Cl	dioxane/ water	15	70	b.p. 50/0.40[e]	45/0,05[17]	181 + 183 (M^+), 135 + 137, 107 + 109, 90 + 92
e	CH_3	$CH_2-CH_2-COOCH_3$	Cl	methanol	10	95	b.p. 80/0.20[e]	$C_6H_{10}ClNO_4$ (195.6)	195 + 197 (M^+), 164 + 166, 149 + 151
f	CH_3	$CH_2-CH_2-COOCH_3$	Br	methanol	10	95	b.p. 85/0.20[e]	$C_6H_{10}BrNO_4$ (240.1)	239 + 241 (M^+), 208 + 210, 193 + 195, 161 + 163, 133 + 135
g	CH_3		Cl	methanol	15	95	b.p. 115/0.20[e]	$C_8H_{14}ClNO_4$ (223.7)	223 + 225 (M^+), 222 + 224, 121 + 123, 101, 85
h	CH_3		Br	methanol dioxane/ water	20 30	72 95	b.p. 125/0.20[e]	$C_8H_{14}BrNO_4$ (268.1)	267 + 269 (M^+), 266 + 268, 165 + 167, 101, 85
i			Cl	dioxane/ water	45	54	m.p. 78–80	$C_8H_{12}ClNO_4$ (221.6)	221 + 223 (M^+), 175 + 177, 139
j			Cl	dioxane/ water	15	75	–[f]	$C_{13}H_{22}ClNO_6$ (323.8)	323 + 325 (M^+), 322 + 324, 238 + 240, 222 + 224, 101, 85
k			Br	dioxane/ water	15	72	b.p. 175–180/0.10[e]	$C_{13}H_{22}BrNO_6$ (368.2)	367 + 369 (M^+), 282 + 284, 266 + 268, 101, 85
l		$CH_2-CH_2-COOCH_3$	Cl	methanol dioxane/ water	15 10	90 95	b.p. 145–150/0.30[e]	$C_{11}H_{18}ClNO_6$ (295.7)	295 + 297 (M^+), 264 + 266, 194 + 196, 101, 85
m		$CH_2-CH_2-COOCH_3$	Cl	methanol	10	65	b.p. 160–165/0.30[e]	$C_{12}H_{20}ClNO_6$ (309.7)	309 + 311 (M^+), 308 + 310, 208 + 210, 161 + 163, 101, 85
n		$CH_2-CH_2-COOCH_3$	Cl	methanol	10	44	–[f]	$C_{17}H_{22}ClNO_6$ (371.8)	371 + 373 (M^+), 325 + 327, 270 + 272, 224 + 226, 191, 101, 85
o		$CH_2-CH_2-C\equiv N$	Cl	methanol dioxane/ water	15 10	25 90	–[f]	$C_{11}H_{17}ClN_2O_4$ (276.7)	276 + 278 (M^+), 277 + 275, 230 + 232, 174 + 176, 101, 85
p	 $-CH_2O-\overset{C_6H_5}{\underset{H}{C}}-OCH_2-$		Cl	methanol	30	90	*cis:* m.p. 67–69.5 *trans:* m.p. 76–76.5	$C_{10}H_{10}ClNO_4$ (243.6)	243 + 245 (M^+), 197 + 199, 161, 105
q	CH_3	CH_2OH	Cl	methanol	20	85	b.p. 95–100/0.3[e–g]		109 + 111, 93 + 95
r	 $-(CH_2)_4-\overset{O}{\overset{\|}{C}}-$		Cl	dioxane/ water	20	0			
s		$CH_2-COOC_2H_5$	Cl	methanol	20	0			

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[a] Yield of isolated pure product.

[b] The microanalyses were in good agreement with the calculated values: C ±0.2, H ±0.1, Cl ±0.10, Br ±0.15.

[c] Recorded on a AEI MS 50 instrument.

[d] Lit.[1] b.p. 73–75/50.

[e] Bulb to bulb distillation.

[f] Purified by column chromatography on silica gel.

[g] Lit.[18] m.p. 114.

pure dioxane (20 ml) under an Argon atmosphere. Argon is bubbled through the solution of 5–10 min at room temperature; then, *N*-chloro- or *N*-bromosuccinimide (24 mmol) is added all at once. The reaction is exothermic and the yellow nitronate solution bleaches instantly. Stirring is continued at room temperature for the time indicated in Table 1. The solvent is then partially removed under atmospheric (**2a, b, d, e**) or reduced pressure, water (100 ml) is added, and the pH is adjusted to 6–7 by addition of 5% hydrochloric acid. The solution is then extracted with dichloromethane (3 × 20 ml) and the combined extracts are washed with water (2 × 20 ml), dried with sodium sulfate, and evaporated under atmospheric (**2a, b, d, e**) or reduced pressure to give the practically pure *gem*-halonitro compound **2**. Analytically pure compounds are obtained by column chromatography on silica gel (pentane/ether or dichloromethane), distillation, or crystallization from methanol.

Table 2. Spectral Data of Compounds **2**

2	IR ($CHCl_3$) ν[cm^{-1}]	^{1}H-NMR ($CDCl_3$)[a] α[ppm]
a	(neat): 1560 (NO_2)	2.11 (s, 6H, $2C\underline{H}_3$)
b	1550 (NO_2)	2.28 (s, 6H, $2C\underline{H}_3$)
c	1550 (NO_2)	1.07–1.88 [m, 6H, $(C\underline{H}_2)_3$]; 1.88–2.54 (m, 4H, $C\underline{H}_2CClNO_2C\underline{H}_2$)
d	1580 (NO_2); 1760 (COOR)	1.31 (t, 3H, J = 6.5 Hz, $OCH_2C\underline{H}_3$); 2.24 (s, 3H, $C\underline{H}_3$); 4.32 (q, 2H, J = 6.5 Hz, $OC\underline{H}_2CH_3$)
e	1560 (NO_2); 1730 (COOR)	2.06 (s, 3H, $C\underline{H}_3$); 2.55 (m, 4H, $C\underline{H}_2C\underline{H}_2$); 3.66 (s, 3H, $OC\underline{H}_3$)
f	1550 (NO_2); 1730 (COOR)	2.22 (s, 3H, $C\underline{H}_3$); 2.64 (m, 4H, $C\underline{H}_2C\underline{H}_2$); 3.68 (s, 3H, $OC\underline{H}_3$)
g	1550 (NO_2)	1.58 (m, 6H, THP); 2.15 (s, 3H, $C\underline{H}_3$); 3.65 (m, 2H, $OC\underline{H}_2CH$); 3.77–4.51 (m, 2H, diast-system[b], $C\underline{H}_2OTHP$); 4.71 (m, 1H, $OC\underline{H}RO$)
h	(neat): 1555 (NO_2)	1.61 (m, 6H, THP); 2.28 (s, 3H, $C\underline{H}_3$); 3.66 (m, 2H, $OC\underline{H}_2CH$); 3.74–4.66 (m, 2H, diast-system[b], $C\underline{H}_2OTHP$); 4.71 (m, 1H, $OC\underline{H}RO$)
i	1550 (NO_2)	1.73 [m, 6H, $(C\underline{H}_2)_3$]; 2.02–2.51 (m, $1H_{ax}$, $\underline{H}CCClNO_2$); 2.57–3.22 (m, $1H_{eq}$, $\underline{H}CCClNO_2$); 4.02 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$)
j	1565 (NO_2)	1.61 (m, 12H, THP); 3.63 (m, 4H, $OC\underline{H}_2CH$); 3.91–4.46 (m, 4H, diast-system[b], $2C\underline{H}_2OTHP$); 4.71 (m, 2H, $2OC\underline{H}RO$)
k	1560 (NO_2)	1.60 (m, 12H, THP); 3.67 (m, 4H, $OC\underline{H}_2CH$); 3.97–4.60 (m, 4H, diast-system[b], $2C\underline{H}_2OTHP$); 4.77 (m, 2H, $2OC\underline{H}RO$)
l	(neat): 1560 (NO_2); 1730 (COOR)	1.62 (m, 6H, THP); 2.36–3.1 (m, 4H, $C\underline{H}_2C\underline{H}_2$); 3.74 (m + s, 5H, $OC\underline{H}_2CH + OC\underline{H}_3$); 3.86–4.46 (m, 2H, diast-system[b], $C\underline{H}_2OTHP$); 4.71 (m, 1H, $OC\underline{H}RO$)
m	1565 (NO_2); 1730 (COOR)	1.31, 1.33, 1.45[c] (3d, 3H, J = 6 Hz, $CHC\underline{H}_3$); 1.61 (m, 6H, THP); 2.37–3.08 (m, 4H, $C\underline{H}_2C\underline{H}_2$); 3.73 (m + s, 5H, $OC\underline{H}_2CH - OC\underline{H}_3$); 4.31–4.91[c] (q, J = 6 Hz + m, 2H, $C\underline{H}CH_3 + OC\underline{H}RO$)
n	1560 (NO_2); 1720 (COOR)	1.62 (m, 6H, THP); 2–3[c] (m, 4H, $C\underline{H}_2C\underline{H}_2$); 2.93–3.44 (m, 1H, $OC\underline{H}CH$); 3.66 (s + m, 4H, $OC\underline{H}_3 + OC\underline{H}CH$); 4.47, 4.51, 4.74, 4.82[c] (m, 1H, $OC\underline{H}RO$); 5.34, 5.42, 5.47, 5.55[c] (m, 1H, $C\underline{H}C_6H_5$); 7.46 (s, 5H, C_6H_5)
o	(in CCl_4): 1560 (NO_2); 2250 (CN)	1.32–1.47[c] (2d, 3H, J = 6 Hz, $CHC\underline{H}_3$); 1.57 (m, 6H, THP); 2.42–3.23 (m, 4H, $C\underline{H}_2C\underline{H}_2$); 3.64 (m, 2H, $OC\underline{H}_2CH$); 4.53–4.64[c] (2q, J = 6 Hz, 1H, $CHC\underline{H}_3$); 4.74 (m, 1H, $OC\underline{H}RO$)
p	1580 (NO_2) (*cis* isomer);	*cis* isomer: 4.44 (s, 4H, $C\underline{H}_2CClNO_2C\underline{H}_2$); 5.56 (s, 1H, $OC\underline{H}C_6H_5O$); 7.44 (s, 5H, $C_6\underline{H}_5$)
	1580 (NO_2) (*trans* isomer)	*trans* isomer: 4.12 (d, 2H, J = −13.3 Hz, $C\underline{H}_{ax}CClNO_2C\underline{H}_{ax}$); 5.08 (d, 2H, J = −13.3 Hz, $C\underline{H}_{eq}CClNO_2C\underline{H}_{eq}$); 5.57 (s, 1H, $OC\underline{H}C_6H_5O$); 7.38 (s, 5H, $C_6\underline{H}_5$)
q	1550 (NO_2); 3400, 3580 (OH)	2.08 (s, 3H, $C\underline{H}_3$); 2.93 (s, 1H, $O\underline{H}$); 3.97 (d, 1H, J = 12 Hz, $C\underline{H}OH$); 4.26 (d, 1H, J = 12 Hz, $C\underline{H}OH$)

[a] Recorded on a Perkin-Elmer R-12A instrument at 60 MHz.

[b] Diastereotopic system.

[c] Data correspond to a mixture of disatereoisomers in a 50 : 50 ratio for **2m** and **2o** and in a 70/30 ratio for **2n**.

Model experiments carried out with **1a, g, j, l** (0.2 mol) gave **2a, g, j, l** in yields similar to those given in Table 1.

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