reacted in 7 mL of HMPA. Titration for bromide ion of the aqueous workup phase showed a 98% yield of the ion. Flash chromatography of the crude product using silica gel and benzene afforded 99 mg (36%) of TLC-pure **3a**: mp 39–40 °C (from petroleum ether/CH_2Cl_2; lit.[16] mp 42 °C); IR (KBr) 2245 (w), 1557 (s), 1379 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 6 H), 4.44 (s, 2 H).

The reaction in DMSO with the soluble K^+/18-crown-6 salt of the nitroalkane yielded 42% (by NMR) of **3a** and the theoretical amount of Br^-; **3a** was further identified by TLC.

α,α-Dimethyl-β-nitrobutyronitrile (3b). Reaction of $MeCH{=}NO_2K$ (from 83 mg of $EtNO_2$ and 129 mg of Me_3COK) with 125 μL of **1** in 3.5 mL of HMPA gave after recrystallization from petroleum ether/CH_2Cl_2 90 mg (57%) of **3b**: white crystals; mp 54.5–57 °C; IR (Nujol) 2240 (m), 1564 (s), 1365 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 and 1.43 (2 s, 6 H), 1.71 (d, J = 7 Hz, 3 H), 4.49 (q, J = 7 Hz, 1 H). Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.68; H, 7.10; N, 19.71. Found: C, 50.49; H, 7.15; N, 19.94.

α,α-Dimethyl-β-nitrononanonitrile (3c). Reaction between $CH_3(CH_2)_5CH{=}NO_2K$ (from 308 mg of 1-nitroheptane and 246 mg of Me_3COK) and 250 μL of **1** in 7 mL of HMPA yielded after Kugelrohr distillation at 195 °C (19 Torr) 276 mg (61%) of **3c**: colorless liquid; IR (neat) 2240 (w), 1558 (s), 1379 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.0 (br, 3 H), 1.0–2.6 (br absorption with 2 s at 1.43 and 1.47, 16 H), 4.33 (dd, J = 3 and 7 Hz, 1 H). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.22; N, 9.51; N, 13.20. Found: C, 61.98; N, 9.54; N, 12.99.

α,α-Dimethyl-β-nitroisovaleronitrile (3d). $Me_2C{=}NO_2K$ (from 192 mg of Me_2CHNO_2 and 255 mg of Me_3COK) and 250 μL of **1** reacted in 7 mL of HMPA. Titration of the aqueous workup phase indicated a 96% yield of Br^-. By GC, **6** was detected in the crude β-nitro nitrile by comparison of the retention time with that of an authentic sample, prepared from $Me_2C(Br)NO_2$ and $Me_2C{=}NO_2K$ in DMSO;[11b] from the NMR yield of **3d** (82%) and the chromatographic peak areas for **3d** and **6**, assuming an equal detector response for both compounds, the yield of dimer amounted to 1%. On recrystallization from petroleum ether/CH_2Cl_2, 228 mg (68%) of **3d** was obtained, mp 191–192 °C (lit.[17] mp 195–196 °C), identified further by IR and ^1H NMR spectra.

The reaction in DMSO yielded 58 and 3% (by NMR) of **3d** and **6** respectively (further identified by GC) and 97% of Br^-. For the reaction in Figure 1, the formation of **3d** was followed by working up aliquots and analyzing by NMR.

α-(1-Nitrocyclohexyl)isobutyronitrile (3e). Reaction of potassium cyclohexanenitronate (from 140 mg of nitrocyclohexane and 131 mg of Me_3COK) with 125 μL of **1** in 3.5 mL of HMPA gave after recrystallization from petroleum ether/CH_2Cl_2 161 mg (76%) of **3e**, mp 105–106 °C (lit.[17] mp 108–109 °C), identified further by IR and ^1H NMR spectra.

Reaction of 1-Bromocyclopentanecarbonitrile with 2-Nitropropane Anion. $Me_2C{=}NO_2K$ (from 155 mg of Me_2CHNO_2 and 206 mg of Me_3COK) and 225 μL of the α-bromo nitrile reacted for 8 h in 6 mL of HMPA. By Kugelrohr distillation were collected two fractions at 105–150 °C (180 Torr; 140 mg) and 200 °C (9 Torr; 51 mg). The latter fraction was 1-(2-nitro-2-propyl)cyclopentanecarbonitrile (**4**, 16%), mp 43.5–44 °C (from petroleum ether; lit.[17] mp 44–45 °C), further identified by IR and ^1H NMR spectra. GC–MS of the first collected fraction showed that it was a mixture of 1-cyclopentenecarbonitrile (**5**, major component), **4**, Me_2CHNO_2, and unreacted α-bromo nitrile. **5**: mass spectrum (70 eV; relative intensity), m/e 93 (24, M^+), 66 (100, M^+ – HCN). In agreement with the presence of **5**, the IR spectrum of the mixture showed peaks at 3060, 2210, and 1612 cm^{-1}, the UV spectrum (EtOH) a maximum at 221 nm [**5**: lit.[18] λ_{max} (EtOH) 216 nm], and the ^1H NMR spectrum a multiplet at δ 6.6. By NMR analysis of the mixture the yield of **5** was 56%; isolation of the product was not attempted.

Reaction of 2-Bromo-2-nitropropane with Isobutyronitrile Anion. NH_2K was prepared under N_2 from 123 mg (3.15 mmol) of potassium and ca. 7 mL of liquid ammonia directly distilled from sodium into the reaction flask. The excess ammonia was then evaporated by a stream of N_2, 10 mL of HMPA was added, and N_2 was bubbled through the mixture for 10 min. This was followed by the addition of 275 μL (3.07 mmol) of freshly distilled Me_2CHCN and, after 30 min, of 325 μL (3.15 mmol) of $Me_2C(Br)NO_2$. After 5 h, the reaction mixture was worked up in the usual manner. The NMR spectrum of the crude product indicated the presence of **6** (12% yield), further identified by GC, which also showed the presence of traces of **3d** (<0.1%).

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Reaction of Secondary Acetylenic Bromides with Sodium Nitrite: Synthesis of 3,5-Alkyl(aryl)-4-nitroisoxazoles

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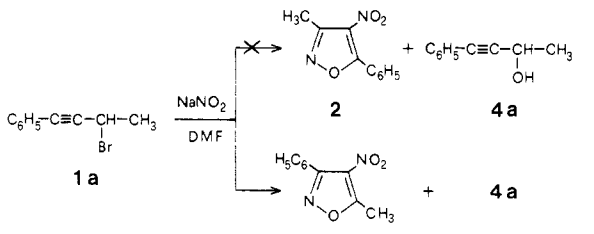
A few years ago, Mechkov and co-workers[1] reported a repetition, with minor modifications, of one of our previous experiments on the synthesis of 3-nitroisoxazoles[2] from primary acetylenic bromides and sodium nitrite in DMF. In addition, they reported that reaction of the secondary acetylenic bromide 3-bromo-1-phenyl-1-butyne (**1a**) under the same conditions gave 3-methyl-5-phenyl-4-nitroisoxazole (**2**). This structure seemed not to agree with our previous experiments, and upon reinvestigation we have found that the product is the isomeric 5-methyl-3-phenyl-4-nitroisoxazole (**3a**).



Our assignment of structure is based on the following: (1) the compound we prepared had the same IR and ^1H NMR spectra and melting point as those reported by Mechkov;[1] (2) our compound showed no melting point depression when mixed with an authentic sample of **3a** prepared in a different way;[3] (3) our compound gave a mass spectrum consistent with our structure; (4) the compound was hydrolyzed by sodium hydroxide to ω-nitroacetophenone oxime (**5**).[4]

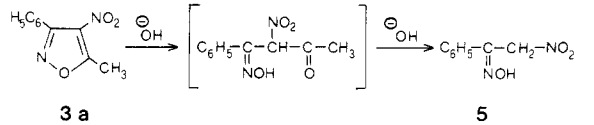


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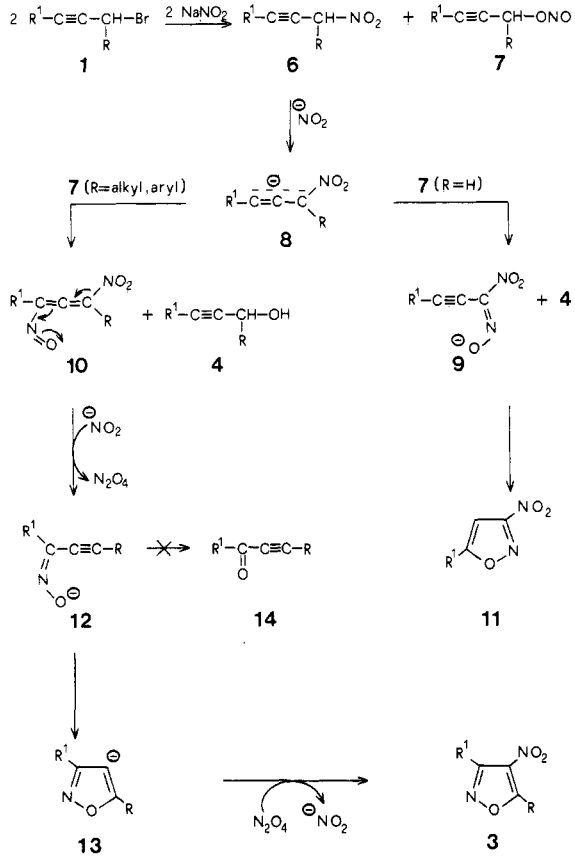
Table I. 3,5-Disubstituted 4-Nitroisoxazoles Prepared (3a-f)[a]

product	ref for 1a-f	time, h	yield,[b] %	mp,[c] °C, or bp, °C/Torr	IR:[d] ν, cm^{-1}	^{1}H NMR ($CDCl_3$): δ	MS: m/e (M^+)
3a	8	48	44[e,f]	48[g]	1610, 830	2.85 (s, 3 H), 7.55 (s, 5 H)	204
3b	9	24	30[f]	79–82/0.2	2960, 1610, 830	0.8–2.4 (m, 9 H), 2.7 (s, 3 H)	184
3c	10	12	36	77/0.3	2965, 1600, 835	1.45 (s, 9 H), 2.7 (s, 3 H)	184
3d	11	18	48	60	1600, 830	2.75 (s, 3 H), 4.3 (s, 2 H), 7.35 (s, 3 H)	218
3e	12	24[h]	32[i]	174–176[g]	1615, 825		266
3f	13	24	46[f]	120/0.2	2975, 1600, 830	1.35 (t, 3 H), 3.15 (q, 2 H), 7.4 (s, 5 H)	218

[a] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.13, N ± 0.22. [b] Yields are yields of isolated products. [c] The products **3a**, **3d**, and **3e** were crystallized from methanol. [d] IR spectra for **3a**, **3d**, and **3e** are in Nujol; for **3b**, **3c**, and **3f** they are neat. [e] HPLC yield = 64%. [f] Yields in alkynols: **4a**, 37%; **4b**, 16%; **4f**, 35%. [g] For **3a**: lit.[1] mp 48 °C. For **3e**: lit.[1] mp 174–176 °C. [h] The reaction was performed in DMF–water, 75%. [i] Yield was calculated on the starting alcohol.

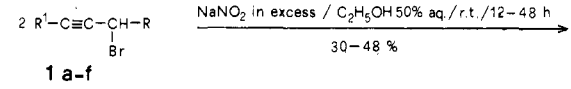
The pathway of the reaction can be explained by postulating that the ambident anion **8** of the nitroalkyne **6** reacts regiospecifically with nitrite **7** at either the 3-position (R = H) to give **9** or the 1-position (R = alkyl, aryl) to give **10**. Structure **9** can cyclize directly to 3-nitroisoxazoles **11**.[2] Structure **10** can react with nitrite ion to give **12** and subsequently 4-nitroisoxazoles **3**. The regiospecificity of the reaction can be rationalized in terms of steric interactions of the incoming nitrite **7** with the R group of the ambident anion **8**.



This mechanism is essentially that proposed by Kornblum and co-workers for the reaction of secondary alkyl bromides with sodium nitrite in DMF.[5] The only change is that intermediate **12** is not converted into ketone **14** but cyclizes at the triple bond through **13** into 4-nitroisoxazole **3**, following the known pattern of formation of 3-nitroisoxazoles[2].

4-Nitroisoxazoles are usually prepared by direct nitration of a free 4-position in the isoxazole ring, but this procedure can also nitrate an aryl substituent on the isoxazole ring. Other routes to 4-nitroisoxazoles have been reported, but they involve intermediates or procedures that are not easy to handle.[3]

We have also found that the reaction of secondary acetylenic bromides with sodium nitrite in aqueous ethanol is a general synthesis of 3,5-alkyl(aryl)-4-nitroisoxazoles.



1 a-f

1,3 and 4	R^1	R
a	C_6H_5	CH_3
b	n-C_4H_9	CH_3
c	t-C_4H_9	CH_3
d	$C_6H_5CH_2$	CH_3
e	C_6H_5	C_6H_5
f	C_6H_5	C_2H_5

3 a-f + **4 a-f**

The reaction has the advantages of being one-pot, of requiring only one easily available organic substrate, and of involving standard workup procedures. Yields are not high, but are useful in practice (Table I).

Experimental Section

Melting points were determined with a Büchi-Tottoli capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 infrared spectrometer. NMR spectra were taken at room temperature in $CHCl_3$-*d* with TMS as internal standard on Varian EM-360L and Varian HA-100 spectrometers. Mass spectra were obtained on a VG-70/70 H instrument at an ionization potential of 70 eV. Column chromatographic separations were performed on Merck silica gel (Kieselgel 60, 230–400 mesh ASTM). Analytical TLC plates from Merck were used.

Reaction between 3-Bromo-1-phenyl-1-butyne (1a) and Sodium Nitrite in DMF. The reaction was performed under the experimental conditions previously reported[1] to give colorless crystals with mp 44–45 °C (hexane) or mp 48 °C (ethanol). There was no melting point depression when the compound was mixed with an authentic sample of 5-methyl-3-phenyl-4-nitroisoxazole (**3a**) prepared in a different way.[3] MS: m/e 204 $(M)^+$, 161 $(M - 43)^+$, 103 $(C_6H_5C{=}N)^+$, 43 $(CH_3C{\equiv}O)^+$. IR (ν, cm^{-1}, Nujol): 1610, 1450, 1430, 1370, 1280, 1190, 830 [lit.[1] IR (ν, cm^{-1}):[6] 1630, 1460, 1430, 1380, 1230, 1190, 840]. ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 3 H, CH_3), 7.55 (m,[7] 5 H, C_6H_5) [lit.[1] ^{1}H NMR[6] δ 2.85 (s, 3 H, CH_3), 7.54 (s, 5 H, C_6H_5)].

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Alkaline Hydrolysis of 5-Methyl-3-phenyl-4-nitroisoxazole (3a). A suspension of 2.04 g (10 mmol) of 5-methyl-3-phenyl-4-nitroisoxazole (**3a**) in 100 mL of 0.5 N sodium hydroxide was refluxed for 1 h. The resulting solution was cooled, acidified with 2 N hydrochloric acid, and extracted with diethyl ether. The organic phase was washed with sodium bicarbonate solution and with water, dried over anhydrous sodium sulfate, then filtered, and evaporated. The residual oil was chromatographed on a silica gel column; elution with benzene–chloroform (9:1) and crystallization from dichloromethane gave 1.26 g (70% yield) of ω-nitroacetophenone oxime (**5**); mp 95 °C (lit.[4] mp 96 °C).

3,5-Disubstituted 4-Nitroisoxazoles (3a–f). General Procedure. To an ice-cold solution of the α-bromoalkyne **1a–f** (10 mmol) in 10 mL of ethanol was added, with stirring, a solution of sodium nitrite (6.9 g, 100 mmol) in 10 mL of water. Stirring was continued at room temperature until the starting compound disappeared on a TLC control. Then 10 mL of water was added, most of the ethanol was removed under vacuum, and the mixture was extracted with ether; the organic phase was washed with water and dried over sodium sulfate. The solvent was evaporated, and the crude residue was fractionated by flash chromatography on a silica gel column (1:50) packed in hexane. 4-Nitroisoxazoles **3a–f** were collected from hexane–benzene (1:1) or benzene fractions and further purified by bulb to bulb distillation or by crystallization. Alkynols **4a–f** were collected from benzene–ethyl acetate (8:2) fractions.

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Registry No. **1a**, 27975-80-0; **1b**, 61783-71-9; **1c**, 72343-39-6; **1d**, 114395-58-3; **1e**, 114395-59-4; **1f**, 29795-81-1; **2**, 75079-84-4; **3a**, 57354-90-2; **3b**, 114395-54-9; **3c**, 114395-55-0; **3d**, 114395-56-1; **3e**, 53215-16-0; **3f**, 114395-57-2; **4a**, 5876-76-6; **4b**, 41746-22-9; **4c**, 17475-10-4; **4d**, 114395-60-7; **4e**, 1817-49-8; **4f**, 27975-78-6; **5**, 21205-24-3; $NaNO_2$, 7632-00-0.

(11) Prepared from corresponding alcohol and PBr_3 in ether: bp 110–112 °C/1 Torr; molecular formula $C_{11}H_{11}BrO$; ^1H NMR (CCl_4) δ 1.91 (d, 3 H, CH_3), 3.6 (d, 2 H, CH_2), 4.6 (m, 1 H, CH), 7.35 (s, 5 H, arom). The starting alcohol 1-phenyl-3-hydroxy-2-pentyne was obtained from benzylacetylene according to Bartlett and Rosen: Bartlett, P.; Rosen, L. *J. Am. Chem. Soc.* **1942**, *64*, 543. Yield 56%; bp 110 °C/0.4 Torr.

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A Convenient Preparation of Ring-Methoxylated Phenylnitromethanes

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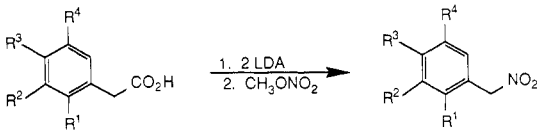
The reaction of benzyl halides with silver nitrite[2-5] and the base-induced alkylation of phenylacetonitriles with alkyl nitrates[6,7] are the only two methods that have been reported for the preparation of phenylnitromethanes, and neither has been demonstrated to be of general synthetic utility for the preparation of analogues in which the aromatic ring is methoxylated. Kornblum and co-workers[4] observed that while benzyl bromide reacts with silver nitrite to give phenylnitromethane, corresponding reaction of *p*-methoxybenzyl bromide gives predominantly the nitrite ester (55%). The alkylation of phenylacetonitriles with alkyl nitrates, a two-step procedure in which the α-nitrophenylacetonitrile from the initial condensation is first isolated and then hydrolyzed and decarboxylated, also has not been used for the preparation of (methoxyphenyl)nitromethanes.

In conjunction with other work, we needed phenylnitromethanes with a methoxylated aromatic ring. The lack of precedent and apparent synthetic limitations of the previously reported methods led us to explore the one-step preparation of phenylnitromethanes through alkylation of the dianions of phenylacetic acids with methyl nitrate.[8] Although it has been shown that dianions of aliphatic acids react with alkyl nitrates to give nitro paraffins,[9] the preparation of phenylnitromethanes was not investigated.

Initially, the phenylacetic acids **1** were reacted with 3 equiv of lithium diisopropylamide (LDA) at −78 °C, quenched with 3 equiv of methyl nitrate, and acidified.



1 2

	R1	R2	R3	R4
a.	H	H	H	H
b.	CH_3O	H	H	H
c.	H	CH_3O	H	H
d.	H	H	CH_3O	H
e.	H	CH_3O	CH_3O	H
f.	CH_3O	H	H	CH_3O

The product mixture was separated by chromatography, furnishing the desired phenylnitromethane **2** and diisopropylnitramine. The latter material was shown to arise from reaction of the excess LDA and methyl nitrate. Decreasing the relative stoichiometry of LDA to 2.2 equiv minimized formation of the nitramine byproduct and permitted, in most instances, direct isolation of product phenylnitromethanes through crystallization and/or distillation.

In initial work on the reaction, we observed that while 2-methoxy- and 2,5-dimethoxyphenylacetic acids gave clear solutions of the dianions, the remaining acids gave suspensions. It has been noted previously[9] that addition of HMPA to dianion suspensions effects their solution and gives improved yields on subsequent reaction with electrophiles. Generation of phenylacetic acid dianions in the presence of added HMPA gave homogeneous solutions, which on reaction with methyl nitrate and subsequent acidification resulted in the best yields of phenylnitromethanes. Irrespective of the presence of HMPA, nearly identical yields of phenylnitromethanes were obtained from dianions of acids that initially gave clear solutions.

In summary, condensation of the dianions of ring-methoxylated phenylacetic acids with methyl nitrates provides a general, one-step procedure to the corresponding phenylnitromethanes in good yields.

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