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Convenient preparation of arylnitromethanes by oxidation of benzaldoximes with urea hydrogen peroxide

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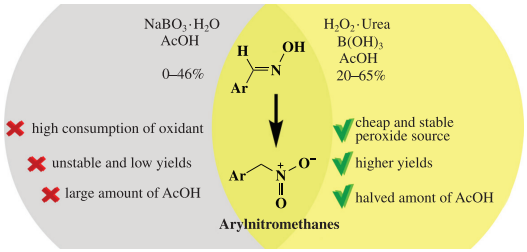
Arylnitromethanes were prepared by oxidation of aldoximes with sodium perborate or with urea hydrogen peroxide in the presence of boric acid. The use of urea hydrogen peroxide complex provides better and more stable yields of nitro compound and allows one to halve an acetic acid consumption. Only *E*-aldoximes are oxidized to arylnitromethanes while *Z*-isomers are transformed into complex mixtures not containing arylnitromethanes.



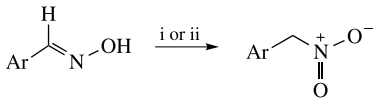
Keywords: arylnitromethanes, aldoximes, oxidation, perborate, urea, hydrogen peroxide.

Arylnitromethanes (ANMs) are valuable synthetic intermediates used in the synthesis of aryl-substituted aliphatic and heterocyclic compounds, *e.g.*, 1,2-diaryl-2-aminoethanols, 2,3-diarylmorpholines, and triarylimidazolines.[1,2] In previous works of authors, ANMs were used for the preparation of 1,2-diarylnitroethenes, 3,4-diarylpyrroles[3] and 3,4-diarylisoxazoles[4] which are strong tubulin polymerization inhibitors.

Diverse synthetic methods have been employed for the preparation of ANMs.[5–10] 3,4,5-Trimethoxyphenylnitromethane **2i** was obtained as one of the products by nitration of 3,4,5-trimethoxytoluene in HNO_3–AcOH mixture with yields up to 35%.[6(a)] However, the radical nitration of the toluene methyl group gives complex mixtures which include aryl nitration and oxidation products.[6] Reactions of benzyl halides with silver nitrite (the Victor Meyer reaction) or with sodium nitrite (the Kornblum modification) are among the most useful pathways to ANMs.[5,7] In 1955, Kornblum reported that while *p*-nitrobenzyl and benzyl bromides reacted with silver nitrite to give ANMs, the analogous reaction of *p*-methoxybenzyl bromide gave predominantly the nitrite ester (55%).[7] In this regard it has been proposed[7,8(a)] that the Meyer reaction is not applicable to the production of ANMs bearing donor substituents. Palladium-catalyzed nucleophilic substitution in aryl halides with nitromethane[9] was not effective with the application of conventional phosphines as ligands, and the use of expensive and easily oxidizable XPhos was required. Alkaline nitration of arylacetic acids[8] provided high yields of ANMs, however expensive reagents such as NaH, LDA, or $NaN(SiMe_3)_2$ and explosive $MeONO_2$ were used. Conversion of carbonyl to nitro group (retro-Nef reaction) is achieved *via* oximes using various peroxide oxidants. To improve the yields of nitro compounds and to reduce the by-product formation, various oxidant systems were investigated: urea hydrogen peroxide complex (UHP) in trifluoroacetic acid,[10(a)] UHP in the presence of ammonium perruthenates,[10(b)] MCPBA,[10(c),(d)] oxone,[10(e)] and peracetic acid.[10(f),(g)] Olah and co-workers[10(h)] have shown that sodium perborate oxidized benzaldehyde oxime **1a** to phenylnitromethane **2a**. Sodium perborate is a cheap and stable crystalline source of peroxide.[11]

In this work, sodium perborate and UHP were compared in terms of activity and selectivity of oxime oxidation leading to ANMs (Scheme 1, Table 1).

The sodium perborate oxidation was carried out† according to the Olah method[10(h)] when solid sodium perborate was portionwise added to a solution of oxime **1** in acetic acid. Nitro compound yield variability may be attributed to the presence of metals traces in sodium perborate oxidant. Under standard conditions, when UHP was used instead of sodium perborate, the oxidation was slow and complete conversion of the starting oxime was difficult to achieve, resulting in a complex reaction mixture. Purity of phenylnitromethane isolated from oxidation



1a–l **2a–l**

a Ar = Ph
b Ar = 4-BrC_6H_4
c Ar = 3-$O_2NC_6H_4$
d Ar = 4-$O_2NC_6H_4$
e Ar = pyridin-4-yl
f Ar = 4-$MeOC_6H_4$
g Ar = 4-$EtOC_6H_4$
h Ar = 3,4-$(MeO)_2C_6H_3$
i Ar = 3,4,5-$(MeO)_3C_6H_2$
j Ar = 2,5-$(MeO)_2$-3,4-$(OCH_2O)C_6H$
k Ar = 4-HOC_6H_4
l Ar = 4-MeO-3-$O_2NC_6H_3$

Scheme 1 *Reagents and conditions*: i, $NaBO_3 \cdot n H_2O$, AcOH, 40–60 °C, 6–10 h; ii, H_2O_2·urea, $B(OH)_3$, AcOH, 50–60 °C.

† *General procedure for sodium perborate oxidation*. Oxime **1a–l** (60 mmol) was dissolved in glacial acetic acid (300 ml) with stirring and heating up to 60 °C. Powdered sodium perborate (360 mmol) was then added within 30 min, and the mixture was stirred at 60 °C for 6 h and left overnight at room temperature. The mixture was poured into distilled water (400 ml), extracted with dichloromethane (3×45 ml), the combined organic extracts were washed with NaOH (1 N aq., ~2×45 ml) until pH 9 (usually accompanied with colour changing), and finally washed with water until pH 7. Benzoic acid was filtered off (if needed), and the solution was dried over $MgSO_4$. The solvent was removed *in vacuo* to afford ANMs **2a–l** as oils or crystalline materials (further purifying was required in exceptional cases, for details, see Online Supplementary Materials).

Table 1 Preparation of arylnitromethanes by oxidation of oximes.

Entry	Oxime	Ar	Oxidant[a]	*T*/°C	*t*/h	Yield of **2** (%)
1	*E*-**1a**	Ph	Perborate	60	6	46
2	*E*-**1a**	Ph	Perborate	40	8	14
3	*E*-**1a**	Ph	UHP	60	6	21
4	*E*-**1a**	Ph	UHP, $B(OH)_3$	60	6	57
5	*E*-**1a**	Ph	UHP, $B(OH)_3$	60	8	66
6	*E*-**1b**	4-BrC_6H_4	Perborate	60	6	43
7	*E*-**1b**	4-BrC_6H_4	UHP, $B(OH)_3$	60	6	45
8	*E*-**1b**	4-BrC_6H_4	UHP, $B(OH)_3$	55	10	55
9	*E*-**1c**	3-$O_2NC_6H_4$	Perborate	40	7	6
10	*E*-**1c**	3-$O_2NC_6H_4$	UHP, $B(OH)_3$	60	6	29
11	*E*-**1d**	4-$O_2NC_6H_4$	Perborate	60	6	16
12	*Z*-**1d**	4-$O_2NC_6H_4$	Perborate	60	6	0
13	*E*-**1d**	4-$O_2NC_6H_4$	UHP, $B(OH)_3$	60	6	26
14	*E*-**1e**	pyridin-4-yl	UHP, $B(OH)_3$	60	6	0
15	*E*-**1f**	4-$MeOC_6H_4$	Perborate	60	6	36
16	*Z*-**1f**	4-$MeOC_6H_4$	Perborate	60	6	2
17	*E*-**1f**	4-$MeOC_6H_4$	Perborate	60	6	32
18	*E*-**1f**	4-$MeOC_6H_4$	Perborate	55	9	43
19	*E*-**1f**	4-$MeOC_6H_4$	UHP, $B(OH)_3$	60	6	35
20	*E*-**1g**	4-$EtOC_6H_4$	Perborate	50	6	39
21	*E*-**1g**	4-$EtOC_6H_4$	UHP, $B(OH)_3$	50	6	13
22	*E*-**1h**	3,4-$(MeO)_2C_6H_3$	UHP, $B(OH)_3$	55	9	17
23	*E*-**1i**	3,4,5-$(MeO)_3C_6H_2$	UHP, $B(OH)_3$	55	9	2
24	*E*-**1j**	2,5-$(MeO)_2$-3,4-$(OCH_2O)C_6H$	UHP, $B(OH)_3$	55	9	5
25	*E*/*Z*-**1k**[b]	4-HOC_6H_4	Perborate	60	6	0
26	*E*-**1l**	4-MeO-3-$O_2NC_6H_3$	Perborate	60	10	10
27	*E*-**1l**	4-MeO-3-$O_2NC_6H_3$	UHP, $B(OH)_3$	60	6	41

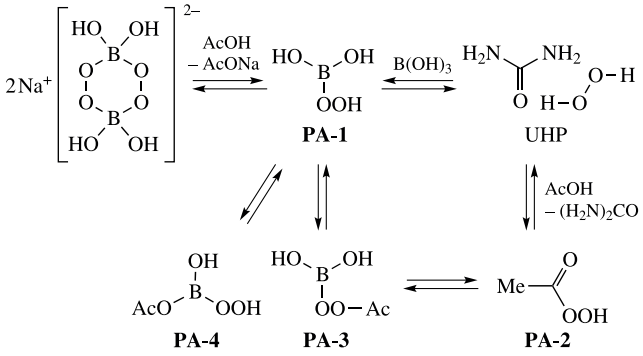
[a] Perborate is sodium perborate, $Na_2[B_2O_4(OH)_4]\cdot 6H_2O$; UHP is urea hydrogen peroxide ($H_2O_2\cdot NH_2CONH_2$), glacial AcOH was the solvent in all reactions. [b] ~97 : 3 *E*/*Z*-isomer mixture.

with UHP was about 20%, which is consistent with the literature data.[10(a)] However, according to Vara[10(d)] and McKillop,[11] UHP reacted with trifluoroacetic anhydride to afford peroxytrifluoroacetic acid, which oxidized aldoximes to nitro compounds with good yields.

Here, cheap and easy to handle boric acid was used instead of trifluoroacetic anhydride.‡ In the optimized procedure, boric acid was dissolved in acetic acid at 100 °C, this solution was cooled to 60 °C followed by portionwise addition of aldoxime and then UHP (see Table 1). In oxidation with UHP–$B(OH)_3$–AcOH system, the amount of acetic acid was halved, higher yields of the target nitro compounds were achieved, and reproducibility of the yields was improved.

We observe the same correlation between ANM yields and aryl nature using both oxidizing systems. It indicates that the active oxidizing molecule could be the same for these two systems.The crystal structure of sodium perborate established by X-ray diffraction includes centrosymmetric $[B_2O_4(OH)_4]^{2-}$ anion.[12(a)] Upon dissolution of perborate in alkaline media, $[B(OH)_3(OOH)]^-$ was registered by ^{11}B-spectroscopy.[12]

In acidic medium, perboric acid **PA-1** is likely the first product after protonation of sodium perborate (Scheme 2), however the perboric acid oxidant molecule does not look like a sufficiently active agent. In the mixture of AcOH, UHP, and $B(OH)_3$, formation of peracetic acid **PA-2** seems possible.

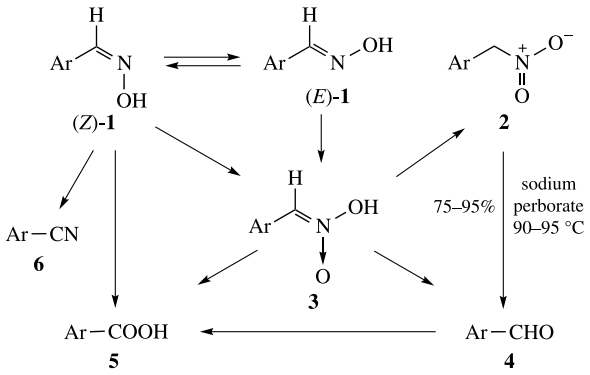


Scheme 2

Peracetic acid **PA-2** is documented agent for oxidation of aldoximes,[10,13] however mixtures of UHP and AcOH have weak activity in the absence of boric acid. Other acylperboric agents such as **PA-3** and **PA-4** have also been considered as active oxidizing species (see Scheme 2), but sufficient data of ^{11}B-spectroscopy and other physicochemical methods have not been published yet.[14]

As seen from Table 1, the output of ANM preparation is highly substrate dependent. Oxidation of pyridine-3-carbaldehyde and 4-hydroxybenzaldehyde oximes **1e**,**k** did not lead to corresponding ANM **2e**,**k** (entries 14, 25). The yields are lower in the case of donor aryls due to oxidation of the polymethoxyaryl groups (entries 22–24). In these cases, lowering the temperature might improve the reaction outputs, however the temperature cannot be lower than 40 °C. The yields are also lower in the case of substrates with strong acceptor aryls when incomplete conversion of the aldoxime was observed (entries 9–13). Increasing the temperature cannot be recommended because ANMs are readily oxidized at 95 °C with sodium perborate to the corresponding aldehydes **4** in

‡ *General procedure for oxidation by UHP–B(OH)$_3$ system*. Boric acid (310 mmol) was dissolved in glacial acetic acid (150 ml) at 100–110 °C. After cooling to 60 °C, the corresponding oxime **1a–l** (62 mmol) was dissolved in the prepared suspension. Powdered UHP (372 mmol) was added by portions under stirring within ~40 min, and the mixture was stirred at 60 °C for 6 h (see Table 1) and left overnight at room temperature. Work up was the same as described in procedure with sodium perborate.



Scheme 3

70–95% yields (Scheme 3).[10(*f*)] Hence, the temperature range of 40–75 °C is optimal for obtaining ANMs.

In one of the pioneering works on oxidation of oximes[10(*i*)] an *aci*-form of nitro compound **3** was suggested as initial product of oxidation, then *aci*-form **3** isomerizes to nitro compound **2** (see Scheme 3). *aci*-Forms **3** are the main intermediates in the Nef reaction leading to carbonyl compounds **4**.[15] Aldehydes **4** and acids **5** formed by the Nef reaction are common by-products of oxime oxidation. Perborate oxidation of oximes at 90–95 °C gives aldehydes **4** in yields of 75–95%.[10(*b*),11,13] Also, perborate oxidation always affords 1–5% of nitriles **6** as by-products. *Z*-Aldoximes are likely source of nitriles since water elimination occurs as a *trans*-process whereas *E*-aldoximes cannot lose the water molecule in this way.[16]

In order to obtain the best yields of ANMs **2**, pure *E*- and *Z*-aldoximes were prepared by standard procedures. A reaction of aldehydes with hydroxylamine carried out in a highly alkaline solution produces almost pure *E*-aldoximes. According to the standard procedure using concentrated HCl,[17] *p*-nitro- and *p*-methoxybenzaldoximes *E*-**1d**, *E*-**2f** were converted to the corresponding *Z*-forms. The structure of oximes is easy to control by ^{1}H NMR because both oxime CH- and OH-signals are visible in DMSO-d_6 (but not in $CDCl_3$). Quite unexpectedly, when oximes *Z*-**1d**, *Z*-**1f** were subjected to the oxidation, yields of ANMs **2d**,**f** were 0 and 2%, respectively (see Table 1, entries 12, 16). Hence, to achieve the maximum yields of ANMs, it is optimal to perform the oxime synthesis conditions leading to *E*-forms of aldoximes and to downregulate the content of *Z*-aldoximes.

In summary, ANMs were prepared by oxidation of aldoximes with sodium perborate or urea hydrogen peroxide complex (UHP) in the presence of boric acid. Use of UHP provides better and more stable yields of nitro compound and allows one to halve acetic acid consumption. Only *E*-aldoxime is oxidized to ANMs; the oxidation of *Z*-aldoximes leads to multi-component mixtures without ANMs. The reaction scope is substrate dependent, the maximum yields have been achieved for oximes lacking both strong acceptor and donor groups.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.016.

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