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Nucleophilic Nitration of Arynes by Sodium Nitrite and its Multicomponent Reaction Leading to Double-Functionalized Arenes

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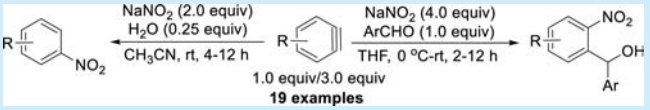
Supporting Information

ABSTRACT: An unusual nucleophilic nitration of arynes by $NaNO_2$ in the presence of water has been developed, and the concept was further demonstrated to accomplish a double functionalization of arynes using a multicomponent reaction protocol to synthesize pharmaceutically important (2-nitrophenyl)methanol derivatives. Such substitution ortho to $-NO_2$ is difficult by other means. The reaction conditions are mild and avoid the use of strong acids, expensive transition metal catalysts, and additives.



Nitroaromatics constitute an important class of compounds that are commonly found in pigments, dyes, advanced materials, polymers, agrochemicals, rubber, specialty chemicals, intermediates, colorants, explosives, and pharmaceuticals.[1−5] They are important building blocks in organic synthesis for accessing complex molecules of pharmaceutical interest.[5] Nitration is at least one of the steps in the whole synthetic process of almost 65% of active pharmaceutical ingredients.[3] In view of the above-mentioned applications, nitration of aromatics is one of the most utilized transformations of industrial interest.[6] Generally it is achieved by strong-acid-catalyzed electrophilic substitution using HNO_3 or by dinitrogen pentoxide,[7] but examples of nucleophilic aromatic nitrations are also known, although not very common initially.[5,8] Poor regioselectivity, poor functional group tolerance under harsh reaction conditions, and overnitration are some of the major issues in nitration processes. Over the past century, several important advances in the area of aromatic nitration have been reported (Figure 1).[1−9] In continuation of our research interest in the development of novel and original methodologies using arynes as reactive intermediates,[10] we were curious to see whether an alternative protocol using simple reagents and mild reaction conditions could be developed for the synthesis of nitroaromatics by hitherto unknown nucleophilic nitration of arynes. Herein we present our results on the outcome of our envisioned transformation and its application in a multicomponent reaction.

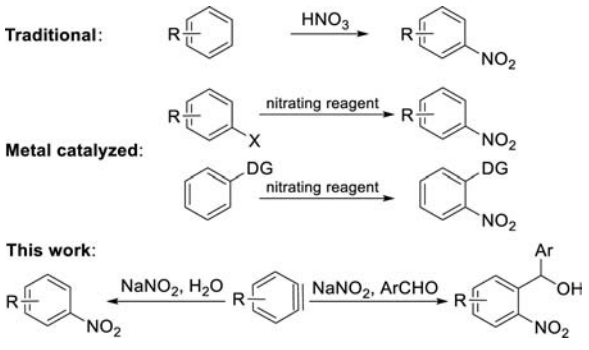


Figure 1. Developments in aromatic nitration.[1−9]

The protocol for the nitration of arynes (generated by Kobayashi's method)[11] was optimized on *o*-silylaryl triflate **1** using several permutations and combinations (Table 1). Our initial attempts (Table 1, entries 1 and 2) using $NaNO_2$ and CsF as a fluoride source were met with failure. Addition of a small amount of tetrabutylammonium fluoride (TBAF) in the same reaction mixture was found to initiate the reaction (Table 1, entry 3). However, the use of only TBAF as a fluoride source furnished merely a trace amount of nitrobenzene (**2**) (Table 1, entry 4). The yield of nitrobenzene could be improved to 40% by using TBAF as an additive (Table 1, entry 9). At this stage we speculated that the water present in TBAF might facilitate the reaction and that probably TBAF as such has no role as an additive.

Our hypothesis was found to be correct when we performed the reaction using water as an additive. Finally, by the addition of a controlled amount of water as an additive, we obtained nitrobenzene in a maximum 54% yield (Table 1, entry 18). The use of other metal nitrites did not result in any improvement. The scalability of the aryne nitration protocol was tested by performing the reaction of aryne precursor **1** on a 0.5 g scale. The reaction worked very well, furnishing **2** in 60% yield (Table 1, entry 18).

The generality of the optimized protocol was studied on varyingly substituted aryne precursors (Scheme 1). Aryne nitration worked equally well with alkyl-substituted aryne precursors similar to the unsubstituted aryne precursor **1** to furnish the corresponding nitroaromatics in good yields (Scheme 1, **3**−**5**). In the case of halo-substituted aryne precursors, the expected products formed in the complex reaction mixture could not be purified to a purity sufficient for analytical purposes (Scheme 1, **6** and **7**).

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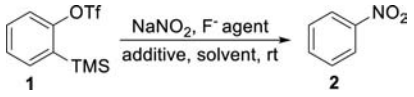
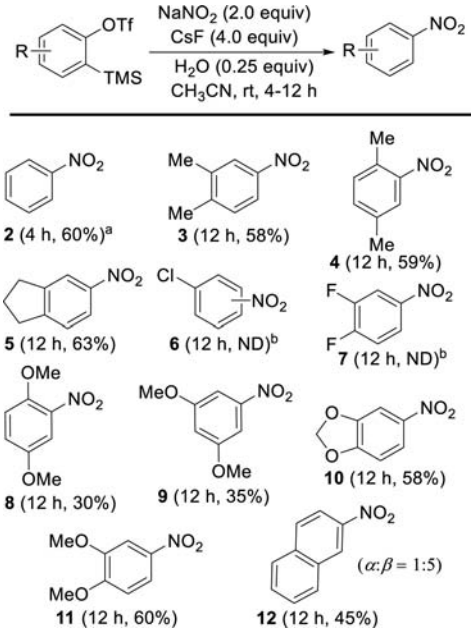
Table 1. Optimization of the Protocol for Nitration of Arynes[a,b]



entry	solvent	equiv of $NaNO_2$	source of F^- (equiv)	additive (equiv)	time (h)	yield (%)[c]
1	CH_3CN	1.2	CsF (3.0)	–	24	trace
2	THF	1.2	CsF (3.0)	–	24	–[d]
3	CH_3CN	1.2	CsF (3.0)	TBAF (0.1)	5	15
4	CH_3CN	1.2	TBAF (2.0)	–	24	trace
5	CH_3CN	3.0	KF (2.0)	18-crown-6 (2.0) + TBAF (0.1)	1	29
6	toluene	3.0	KF (2.0)	18-crown-6 (2.0) + TBAF (0.1)	24	27
7	THF	2.0	KF (3.0)	18-crown-6 (3.0)	5	38
8	CH_3CN	1.5	CsF (2.0)	TBAF (0.1)	12	30
9	CH_3CN	1.5	CsF (4.0)	TBAF (0.1)	7	40
10	CH_3CN	4.0	CsF (4.0)	TBAF (0.2)	7	35
11	CH_3CN	4.0	CsF (4.0)	TBAF (0.2)	24	27
12	CH_3CN	1.5	CsF (4.0)	H_2O (0.2)	24	trace[d]
13[e]	CH_3CN	2.5	CsF (4.0)	–	24	40
14[e]	CH_3CN + H_2O (1:1)	2.5	CsF (4.0)	–	24	–[d]
15[e]	CH_3CN + H_2O (2:1)	2.5	CsF (4.0)	–	24	–[d]
16	CH_3CN	2.0	CsF (4.0)	H_2O (1.0)	24	27
17	CH_3CN	2.0	CsF (4.0)	H_2O (1.0) premixed in CH_3CN	24	40
18	CH_3CN	2.0	CsF (4.0)	H_2O (0.25) in CH_3CN	4	54/60[f]

[a]Reactions were performed on a 50 mg scale of **1**. [b]0.8 mL of solvent. [c]Isolated yields. [d]Aryne precursor remained unconsumed. [e]Bottle-grade acetonitrile. [f]The reaction was performed on a 0.5 g scale of **1**.

Scheme 1. Nitration of Variously Substituted Arynes



[a]The reaction was performed on a 0.5 g scale of **1**. [b]ND: yield not determined.

Electron-donating substituents furnished the corresponding nitro compounds in moderate to good yields (Scheme 1, **8**–**11**). The nitration protocol furnished β-nitronaphthalene (**12**) as the major product in moderate yield and regioselectivity (α:β = 1:5) with an unsymmetrically substituted naphthalene-based aryne precursor.

The above results prompted us to take up the challenge of developing a three-component reaction utilizing aryne, $NaNO_2$, and an electrophile that would provide access to double-functionalized aromatics from arynes.[12] Initially, we screened several electrophiles such as ketones, alkynes, alkenes, arynes, alkyl halides, etc. However, the expected product was observed only in the case of aldehydes. Aldehyde **13** and aryne precursor **1** were used as the substrates for the optimization of the multicomponent reaction (MCR) protocol. Our first attempt at the MCR used the reaction condition developed for the nitration of arynes (Table 1, entry 18). As expected, this did not furnish the MCR product, since it was obvious that acetonitrile and water can quench the carbanion intermediate quickly. Hence, we turned our attention to other reaction conditions (Table 1, entry 7). Optimization of the protocol by varying the ratio of reactants/reagents or by changing the additives (Table 2, entries 2–6) provided the best possible conditions for the MCR, which furnished the desired carbinol **14** in 60% yield (Table 2, entry 3). The suitability of the MCR protocol on a larger scale was demonstrated on representative compound **14** by performing the reaction on 0.5 g of aryne precursor **1**. We observed that on the larger scale, the MCR worked better at room temperature and with less $NaNO_2$ (3 equiv), providing a 62% yield of **14** (Table 2, entry 3). Since the aryne precursor was in excess, it is obvious that the formation of only nitrated product was also observed in all the cases. 2-Substituted nitroaromatic compounds such as carbinol **14** and its congeners obtained from the MCR reaction are of immense pharmaceutical interest and also are precursors to bioactive compounds.[13−15] Hartmann and co-workers reported that these small-molecule inhibitors can repress the formation of biofilms and hence are important in the development of anti-infectives.[14] They have also reported their synthesis using a Grignard reaction, but few other approaches to such carbinols are also known.[16] In view of their importance and to demonstrate the generality of the developed MCR protocol, we studied the substrate scope.

A good yield of the MCR product **14** was obtained for *p*-chlorobenzaldehyde during optimization; however, when the

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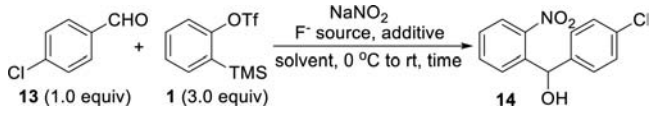
Table 2. Optimization of the MCR[a,b]



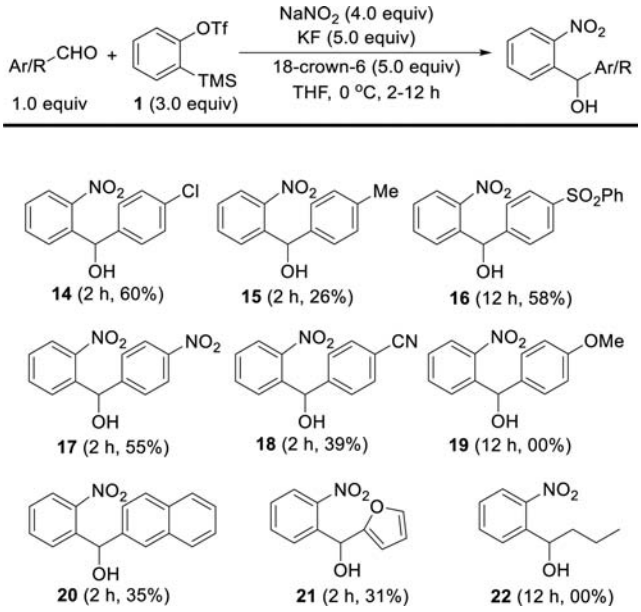
13 (1.0 equiv) 1 (3.0 equiv) 14

entry	solvent	$NaNO_2$ (equiv)	source of F^- (equiv)	additive (equiv)	time (h)	yield (%)[c]
1	CH_3CN	2.0	CsF (4.0)	H_2O (0.25)	12	–
2	THF	3.0	KF (5.0)	18-crown-6 (5.0)	24	44
3	THF	4.0/3.0	KF (5.0)	18-crown-6 (5.0)	2/24	60/62[d]
4	THF	2.0	KF (5.0)	18-crown-6 (5.0)	2	36
5	THF	3.0	KF (5.0)	18-crown-6 (6.0) + $Mg(O^tBu)_2$ (0.2)	24	–
6	THF	3.0	KF (5.0)	18-crown-6 (6.0) + $Cu(OTf)_2$ (0.2)	24	–

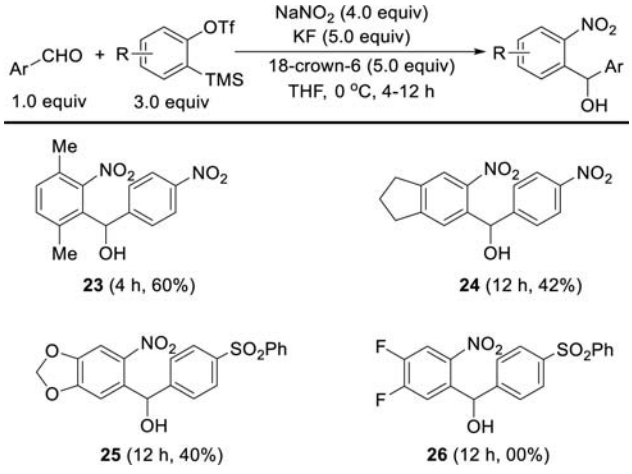
[a]reaction was performed on 50 mg scale of **1**. [b]0.5 mL solvent. [c]isolated yields. [d]reaction was performed on 0.5 g scale of **1** at rt.

para substituent was changed to methyl to obtain carbinol **15**, the yield decreased drastically (Scheme 2). Using aldehydes

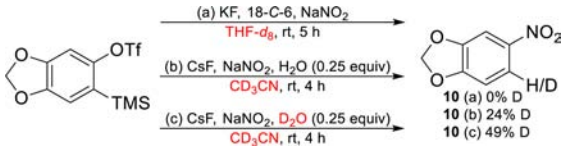
Scheme 2. Aldehyde Substrate Scope of the MCR



Scheme 3. MCR with Selected Aryne Precursors



Scheme 4. Deuterium Incorporation Experiments



substituted with an electron-withdrawing group resulted in improved yields, furnishing carbinols **16**–**18**. In the case of *p*-methoxybenzaldehyde, the corresponding carbinol **19** was not observed. These results clearly show that electronic factors play an important role in this MCR. *β*-Naphthaldehyde and furfuraldehyde also reacted smoothly to provide the corresponding carbinols **20** and **21** in 35% and 31% yield, respectively. However, butyraldehyde did not react at all under the developed reaction conditions, and carbinol **22** was not observed. In all of these MCRs, a varying amount of aldehyde remained unreacted.

The MCR worked well with the unsubstituted aryne precursor **1**. We also performed the reaction on varyingly substituted aryne precursors (Scheme 3) and found that it worked well with alkyl-substituted and electron-rich aryne precursors to furnish carbinols **23**–**25** in moderate to good yields. However, product **26** was not observed when a difluoro-substituted aryne precursor was used as the substrate.

A tentative mechanistic aspect study was performed by means of deuterium incorporation experiments (Scheme 4). Incorporation of deuterium in product **10** was studied by using deuterated solvents. Deuterium incorporation was not observed when the reaction conditions of Table 1, entry 7 were applied on this substrate using THF-d_8 as the solvent (Scheme 4a), suggesting that the moisture present in 18-crown-6 or in the reaction mixture might be the probable source of protons in **10**. This experiment also provides an explanation for the formation of only nitrated products in the MCR. Our standard protocol (Table 1, entry 18) was applied in the presence of CD_3CN and H_2O, which provided **10** with 24% deuterium incorporation (Scheme 4b), suggesting that the solvent CH_3CN also acts as a source of protons. When D_2O was used in combination with CD_3CN, we observed 49% deuterium incorporation (Scheme 4c), indicating that water and the solvent are sources of protons in this reaction.

In summary, we have developed a novel transformation of arynes to obtain nitroaromatics under mild reaction conditions in the presence of water and have also demonstrated an application of the concept in a multicomponent reaction involving aryne, $NaNO_2$, and aromatic aldehyde to synthesize carbinol derivatives of pharmaceutical interest. We believe that both of the protocols developed herein will be useful in late-stage functional group transformations. Currently, we are working on developing MCRs involving other electrophiles and

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exploring the possibility of applying the developed protocol in total syntheses of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01384.

Experimental procedures, spectral and analytical data, and copies of NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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