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Construction of α-methoxyimidoyl ketonitrones via phosphite-mediated addition of α-keto *N-tert*-butanesulfinyl imidates to nitrosoarenes

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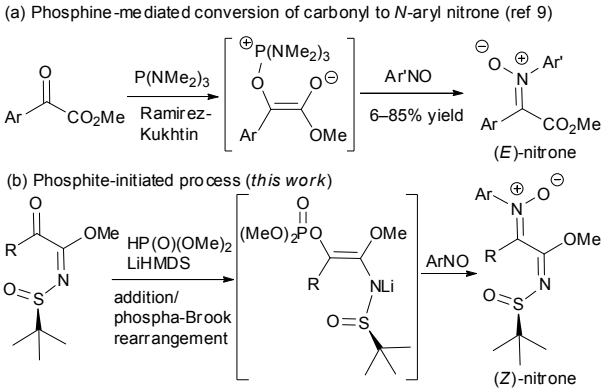
A dimethyl phosphite-mediated addition of α-keto *N-tert*-butanesulfinyl imidates to nitrosoarenes was developed. Nitrosoarenes were successfully used as electrophiles to trap aza-enolate intermediates that were generated from nucleophilic addition of deprotonated phosphite to α-keto *N-tert*-butanesulfinyl imidates and following phospha-Brook rearrangement, allowing efficient construction of ketonitrones with excellent (*Z*)-geometries.

Nitrones are useful precursors in synthetic organic transformations involving dipolar cycloadditions and nucleophilic additions,[1] and they are useful as a spin-trapping reagent for detection of radicals in solution.[2] Traditional preparation of nitrones relies mainly on the condensation of *N*-substituted hydroxylamines with carbonyl compounds[3] and oxidation of secondary amines, *N*-substituted hydroxylamines, or imines.[4] In recent years, new pathways to nitrones have been described based on developments in *N*-alkylation/arylation of oximes[5] and Cope-type hydroamination of allenes with *N*-alkylhydroxylamines[6]. Nitrones are also accessible by using nitrosoarenes as electrophiles to react with carbanions bearing leaving groups such as phenylchloroacetonitrile[7] or α-diazocarbonyl compounds.[8] In 2014, Ashfeld and co-workers reported a $P(NMe_2)_3$-mediated addition of 1,2-dicarbonyl compounds to nitrosoarenes, which constitutes a rare example of an umpolung approach toward (*E*)-*N*-aryl nitrones using carbonyl compounds (Scheme 1a).[9] In this case, polarity inversion at the carbonyl carbon was achieved using Ramirez-Kukhtin reaction[10a–c], which converted 1,2-dicarbonyl compounds to the nucleophilic intermediate oxyphosphonium enolate with the assistance of a trivalent phosphorus reagent.[10d–g]



Scheme 1 Formation of ketonitrones by trapping ketone-derived enolate/aza-enolate intermediates with nitrosoarenes.

Similar polarity inversion at a carbonyl carbon can also be realized via nucleophilic addition of dialkyl phosphite to the keto group of α-ketoesters (or other α-keto acid derivatives), followed by phospha-Brook rearrangement (phosphonate–phosphate rearrangement).[11] This procedure generates α-phosphonyloxy enolates (or aza-enolates)[12] suitable for further intermolecular transformations with electrophiles such as protons,[13] aldehydes/imines,[14] or 1,4-addition acceptors[15] in order to construct diverse molecular structures. Despite being an important electrophile, nitrosoarenes[16] have not been used to intercept the reactive intermediates derived from the phosphite-initiated cascade.

Our continuing interest in the chemistry of Brook rearrangement[17] and chiral imidates[18] prompted us to examine the phosphite-mediated addition of α-keto *N-tert*-butanesulfinyl (*N-t*BS)[19] imidates[20] (a kind of α-keto amide or α-keto ester equivalent) to nitrosoarenes, which would give new access to functionalized ketonitrones (Scheme 1b).

We began our study by examining phosphite-mediated nitrone formation using α-keto (R_S)-*N-tert*-butanesulfinyl imidate **2a** and nitrosobenzene (**3a**) (eq 1, Scheme 2). Addition of lithium bis(trimethylsilyl)amide to the mixture of dimethyl

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† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [Experimental details and spectral data. CCDC 1815452 (**4a**), 1815453 (**4k'**), 1815454 (**4r**), 1815455 (**5**), 1815456 (**6**) and 1815457 (**7**)]. See DOI: 10.1039/x0xx00000x

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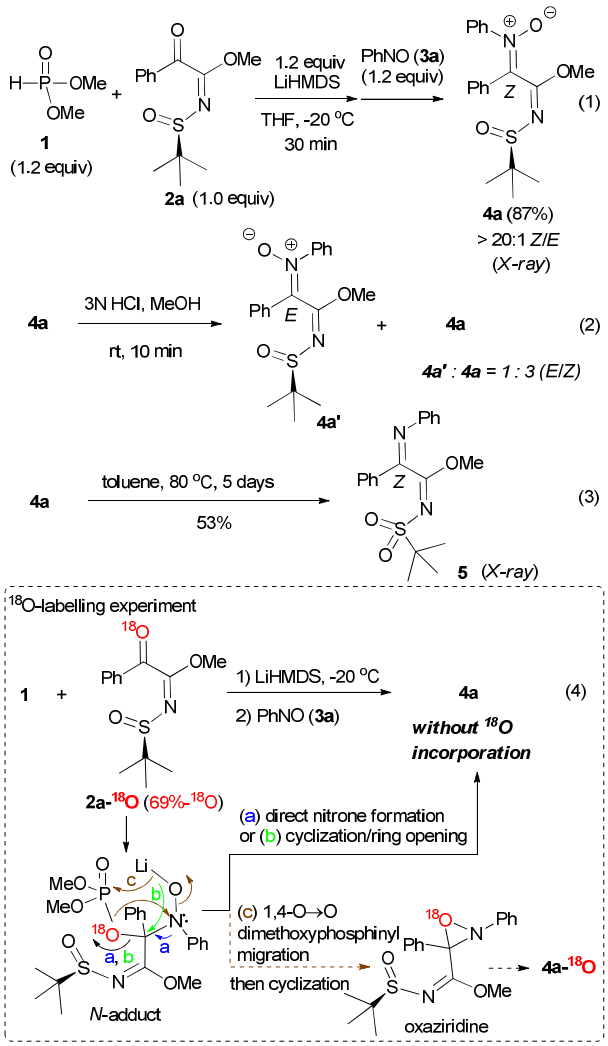

Scheme 2 Initial results for phosphite-mediated addition of α-keto *N-tert*-butanesulfinyl imidates to nitrosoarenes.

phosphite (**1**) and **2a** allowed rapid addition/rearrangement to give reactive α-phosphonyloxy aza-enolate, which underwent nucleophilic addition to nitrosobenzene and subsequent C=N bond formation in which the leaving group was an α-phosphonyloxy group. This process afforded the anticipated α-methoxyimidoyl ketonitrone **4a** in 87% yield. Attempts to trigger this reaction using $P(NMe_2)_3$ (Ashfeld's protocol)[9] rather than $LiP(O)(OMe)_2$ were unsuccessful; no desired product was obtained. Similarly unsuccessful was condensation of **2a** with *N*-phenylhydroxylamine under conditions reported for ketonitrone formation, such as *t*-BuOH at 110 °C[3c] and CF_3CO_2H/4 Å MS.[3b] Further attempts to condense **2a** with BnNHOH or MeNHOH also failed under reported conditions.[3d–e] The compound **2a** may resist the traditional condensation conditions because its *N-tert*-butanesulfinyl imidate group is bulkier than the ester or amide group in common α-keto acid derivatives.

The structure of **4a** was assigned by X-ray crystallography.[21] In this reaction, only the isomer with (*Z*)-geometry for the newly formed C=N bond was observed, in contrast to the preference for (*E*)-geometry in the nitrone derived from methyl benzoylformate (Scheme 1a).[9] Treatment of **4a** with 3 M hydrochloride led to partial isomerization of the C=N bond of the nitrone group (*E*/*Z* = 1:3; eq 2, Scheme 2).[22] The (*E*)-isomer **4a'** was purified by preparative HPLC and fully characterized. This isomerization method was used to identify the (*E*)-isomers for all ketonitrone products **4** in Table 1, ensuring accurate determination of the *Z*/*E* ratio for the cases in Table 1 (*Z*/*E* > 20:1). Luckily, we were able to purify the (*E*)-isomer **4k'** that was produced via acidic isomerization by column chromatography on silica gel, and its crystallization permitted unambiguous assignment of its structure and stereochemistry by X-ray diffraction.[21]

The (*Z*)-nitrone **4a** was stable and showed minimal isomerization under neutral conditions. No *cis*-to-*trans* isomerization was observed after storing **4a** in a refrigerator for 8 months. The only degradation product (~3%) was the α-imino *N-tert*-butanesulfonylimidate **5,** which formed via intramolecular redox transformation. Heating **4a** in benzene at 80 °C for 5 days also gave imine **5** in 53% yield (eq 3, Scheme 2). Proton NMR analysis of the reaction mixture showed the remaining **4a** to be a mixture of geometric isomers (*Z*/*E* ~4:1). The structure of **5** was established by single-crystal X-ray analysis, and the C=N bond of the imine group was found to adopt the *Z* configuration.[21, 23]

Reaction using ^{18}O-labeled α-keto *N-t*BS imidate **2a** yielded nitrone **4a** without effective incorporation of an ^{18}O label into the nitrone group (eq 4, Scheme 2). This result suggests that the reaction proceeds via direct formation of nitrone from the *N*-adduct, or via cyclization through intramolecular displacement of the phosphonyloxy group, which yields oxaziridine and leads to ring opening. The phosphite-mediated reaction of α-keto *N-t*BS imidate with aldehyde has been reported to occur via 1,4-O→O dimethoxyphosphinyl migration in the adduct,[14d] but we were able to rule out this pathway in this case, since we observed no production of ^{18}O-labeled **4a** (Scheme 2).

Next, we surveyed the substrate scope of phosphite-mediated addition of α-keto *N-t*BS imidates to nitrosoarenes. Several nitrosoarenes bearing substitutions on the phenyl group were examined (Table 1), and they gave the corresponding methoxyimidoyl ketonitrones **4b**-**h** (entries 2–8) in good yields, except the 4-acetyl-substituted nitrosobenzene (**3h**), which was obtained in yield of only 36% (entry 8). The low yield is due to incomplete consumption of the addition/rearrangement intermediate generated from **1** and **2a** under standard reaction conditions, as indicated by the substantial amount of α-phosphonyloxy imidate remaining after the reaction was quenched. Diazald® [TsN(Me)N=O], a good reaction partner in Ashfeld's process,[9] was inert in our reaction protocol. The reason for this difference is unclear. Reactions employing α-aryl- or α-heteroaromatic-substituted ketoimidates proceeded well and provided nitrones **4i**-**p** (entries 9–16) in good yields (77–93%). Notably, α-alkyl ketoimidates such as **2i** and **2k** were also suitable substrates, although with diminished yields (entries 17–18). To ensure correct assignment of the ketonitrones derived from α-alkyl

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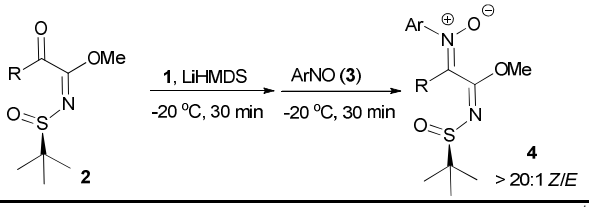
Table 1 Substrate scope for the synthesis of α-methoxyimidoyl ketonitrones[a]

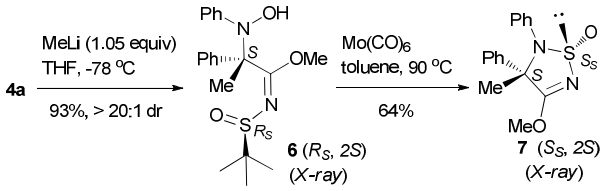


Entry	Imidate **2** (R)	Nitrosoarene **3** (Ar)	Yield of **4** (%)[b]
1	**2a** (Ph)	**3a** (Ph)	**4a**, 87
2	**2a** (Ph)	**3b** (4-ClC_6H_4)	**4b**, 91
3	**2a** (Ph)	**3c** (4-BrC_6H_4)	**4c**, 91
4	**2a** (Ph)	**3d** (2-MeC_6H_4)	**4d**, 78
5	**2a** (Ph)	**3e** (3-MeC_6H_4)	**4e**, 83
6	**2a** (Ph)	**3f** (4-MeC_6H_4)	**4f**, 92
7	**2a** (Ph)	**3g** (4-$MeOC_6H_4$)	**4g**, 80 (80)[c]
8	**2a** (Ph)	**3h** (4-AcC_6H_4)	**4h**, 36
9	**2b** (4-BrC_6H_4)	**3a** (Ph)	**4i**, 87
10	**2c** (4-ClC_6H_4)	**3a** (Ph)	**4j**, 93
11	**2d** (4-FC_6H_4)	**3a** (Ph)	**4k**, 77
12	**2e** (4-MeC_6H_4)	**3a** (Ph)	**4l**, 93
13	**2f** (3-MeC_6H_4)	**3a** (Ph)	**4m**, 88
14	**2g** (4-$MeOC_6H_4$)	**3a** (Ph)	**4n**, 77
15	**2h** (2-naphthyl)	**3a** (Ph)	**4o**, 78
16	**2i** (2-thienyl)	**3a** (Ph)	**4p**, 78
17	**2j** (Et)	**3a** (Ph)	**4q**, 58
18	**2k** ($PhCH_2CH_2$)	**3a** (Ph)	**4r**, 42

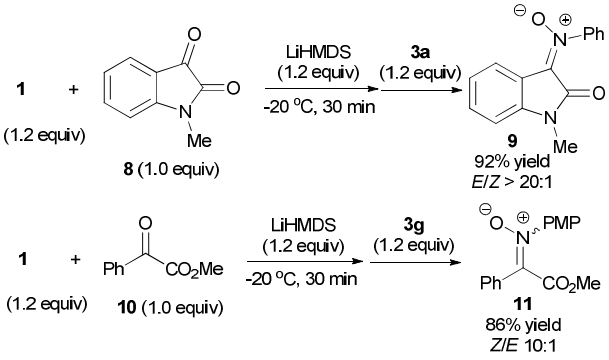
[a] Reaction conditions: **1** (0.24 mmol), LiHMDS (0.24 mmol), **2** (0.20 mmol), and **3** (0.24 mmol) in anhydrous THF (3.0 mL) under argon at −20 °C, unless otherwise noted. The ratio of *Z*/*E* was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Isolated yield after silica gel chromatography. [c] Reaction on 1-g scale.

ketoimidates, **4r** was analyzed by X-ray crystallography, which indicated that the C=N bond of the nitrone group was in the *Z*-configuration, consistent with the configuration in α-aryl ketoimidates.

Chiral α-methoxyimidoyl ketonitrones **4a** were subjected to nucleophilic addition of methyl lithium at −78 °C,[24] which gave α,α-disubstituted α-hydroxyamino imidate **6** in 93% yield with excellent diastereoselectivity (> 20:1 dr, Scheme 3). The absolute configuration of **6** was established as (R_S, *2S*) based on single-crystal X-ray crystallography.[21] The α-tertiary hydroxylamine **6** was then subjected to the conditions of $Mo(CO)_6$-induced reductive N–O bond cleavage.[25] To our surprise, exposure of the N atom in the hydroxyamino group led to intramolecular substitution of *t*Bu in the *tert*-butanesulfinyl group, giving the five-membered cyclic compound **7** in 64% yield. The cyclization proceeded with inversion of the absolute configuration of the S atom,[26] which was confirmed by single-crystal X-ray analysis.[21] Our attempts to achieve dipolar cycloaddition with chiral ketonitrone **4a**



Scheme 3 Transformations of the nitrone **4a**.



Scheme 4 Phosphite-initiated nitrone formation from *N*-methyl isatin **8** and methyl benzoylformate **10**.

were unsuccessful; no cycloaddition reaction occurred with common dipolarophiles such as allyl bromide,[9] ethyl vinyl ether,[3e] or *N*-phenyl maleimide under heating at 80 °C. The α-imino imidate **5** generated from the intramolecular redox reaction (eq 3, Scheme 2) was the only observable product on TLC, with most of the starting material **4a** remaining intact. Elevating the reaction temperature to 110 °C in a sealed tube accelerated the intramolecular redox transformation, but still no cycloaddition products formed.

We then extended this phosphite-mediated protocol to nitrone formation using common non-chiral α-keto amides and esters (Scheme 4). To our delight, the reaction of the isatin derivative **8** proceeded smoothly and provided the ketonitrone **9** in 92% yield with *E*/*Z* >20:1, which is superior to the results reported for Ashfeld's protocol (41% yield, *E*/*Z* >11:1).[9] In the case of methyl benzoylformate **10**, our approach led to similar yield as Ashfeld's protocol (86% *vs* 85%), but higher *Z*/*E* ratio (10:1 *vs* 1:1).[27]

In summary, a dimethyl phosphite-mediated protocol for synthesis of ketonitrones has been described. The phosphite addition/rearrangement cascade allows α-keto *N*-*tert*-butanesulfinyl imidates to function as Darzens-like reagents to react with electrophilic nitrosoarenes. A range of chiral α-methoxyimidoyl ketonitrones that are difficult to access using known methods have been prepared with excellent (*Z*)-geometries. The described protocol can also be applied to the synthesis of ketonitrones derived from other α-keto acid derivatives such as isatins and α-keto esters.

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Conflicts of interest

There are no conflicts to declare.

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A dimethyl phosphite-mediated addition of α-keto *N*-*tert*-butanesulfinyl imidates to nitrosoarenes leads to efficient construction of α-methoxyimidoyl ketonitrones with excellent (*Z*)-geometry