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A modular approach to α , β -unsaturated *N*-aryl ketonitrones

Tyler S. Hood, C. Bryan Huehls, Jiong Yang*

Department of Chemistry, Texas AM University, College Station, TX 77843-3255, USA

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Nitrones are widely recognized as important building blocks in organic synthesis. Much of this popularity can be traced to their facile [3+2] cycloadditions with alkene and alkyne dipolarophiles to form products such as isoxazolidines and 2,3-dihydroisoxazoles that not only are common structural components but are also valuable intermediates to other important motifs.¹ Nitrones are also excellent electrophiles for reactions with organometallic reagents to give nitrogen-containing compounds and enantioselective versions of these transformations are known.² Utility of nitrones in transformations other than dipolar [3+2] cycloadditions and alkylations has been reported as well.³ These include a recent discovery by our laboratory that α,β -unsaturated *N*-aryl ketonitrones, when combined with activated alkynes, afforded C3-quaternary indolenines with concomitant formation of up to two contiguous quaternary and tertiary chiral centers (Scheme 1).⁴ The ketonitrones employed in our study were prepared by reaction of aryl nitro compounds with crotylmagnesium chloride as described by Bartoli to give α,β -unsaturated N-aryl ketonitrones that are β -unsubstituted,⁵ or by reaction of silvl dienolates and excess of nitrosobenzene as we have previously reported to give those with β -alkoxycarbonyl substituents (Scheme 2).⁶ To the best of our knowledge, no other approaches to these species have been reported. Our interest in expanding the power and scope of this transformation and exploring other potential reactivities of α , β -unsaturated N-aryl ketonitrones required access to these species with diverse substitution patterns. This led us to consider developing a general and synthetically useful approach to α,β -unsaturated N-aryl ketonitrones beginning from readily available starting materials since the current methods would only allow synthesis of these species with

ABSTRACT

A modular approach to α , β -unsaturated *N*-aryl ketonitrones has been developed. Specifically, condensation of anilines and enals followed by alkylation of the resulting α , β -unsaturated imines provided *N*-allyl anilines, which were subjected to oxidation with Oxone[®] to form α , β -unsaturated *N*-aryl ketonitrones. This modular approach is general and provides rapid access to diversely substituted α , β -unsaturated *N*-aryl ketonitrones with a single purification step in good yields.

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Scheme 1. Reaction of α , β -unsaturated *N*-aryl ketonitrones and activated alkynes.

limited substitution. Such an approach would allow us to acquire knowledge of the general stability of these relatively unexplored species, examine their reactivity with dipolarophiles, and explore their potential as reagents in other transformations.

A number of methods have been known for the preparation of nitrones,⁷ but the most convenient and commonly used are by condensing N-monosubstituted hydroxylamines and carbonyl compounds or by oxidation of the corresponding hydroxylamines, imines, or amines.⁸ The reaction of *N*-substituted hydroxylamines and aldehydes is typically facile and gives aldonitrones in high yields. However, except for the intramolecular variant, condensation of N-substituted hydroxylamines and ketones typically requires harsh conditions and is of limited scope. Indeed, despite sporadic reports of condensing *N*-alkyl hydroxylamines and α , β unsaturated ketones to give the corresponding ketonitrones,⁹ direct condensation of *N*-aryl hydroxylamines and α,β -unsaturated ketones had been unsuccessful.¹⁰ Thus, our efforts focused on developing an approach based on oxidation of *N*-allyl anilines. which could be synthesized in a modular approach by condensing anilines and α , β -unsaturated aldehydes to give *N*-allylideneanilines, followed by alkylation with organometallic reagents. This method was successfully applied in the synthesis of a range of α , β -unsaturated ketonitrones as shown in Table 1.



^{*} Corresponding author. Tel.: +1 979 845 2889; fax: +1 979 845 4718. *E-mail address*: yang@mail.chem.tamu.edu (J. Yang).

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Scheme 2. Approaches to α , β -unsaturated *N*-aryl ketonitrones.

Table 1

Synthesis of α , β -unsaturated *N*-aryl ketonitrone **3**

	R ² R ¹	$\bigwedge_{\text{o}} \begin{array}{c} \text{ArNH}_{2}, \text{MgSO}_{4}, \\ \text{ether}; \\ \text{R}^{3}\text{Li, ether} \end{array} \xrightarrow{R^{2}} R^{1}$	NHAr Oxone, a NaHCO ₃ R ³	$\xrightarrow{Ar_{N}}_{R} \xrightarrow{Ar_{N}}_{N} \xrightarrow{Ar_{N}}_{N} \xrightarrow{Ar_{N}}_{R} $	
Entry	Aldehyde 1	N-Allyl aniline 2 (yield)		α,β -Unsaturated <i>N</i> -aryl ketonitr	one 3 (yield, <i>E:Z</i> ratio)
1	Ph	Ph_NH Ph	2a (79%)	Ph、+,O ⁻	3a (80%, 3.6:1)
2		2'-tolyl NH	2b (91%)	2'-tolyl、+,O ⁻ Ph	3b (67%, 2.7:1)
3		4'-tolyl NH	2c (44%)	4'-tolyl \ +, O N Ph	3c (62%, 3.7:1)
4		4'-Cl-Ph NH	2d (64%)	4'-Cl-Ph、+./O ⁻ N Ph	3d (34%, 2:1)
5		Ph_NH Ph	2e (78%)	$\frac{Ph_{N}^{+,O}}{N}$	3e (22%, 3.3:1)
6		Ph _{NH} Phn-Bu	2f (71%)	Ph、+,·O ⁻ Ph	3f (82%,2:1)
7		Ph`NH Ph Ph	2g (88%)	Ph	3g (52%, ≥5:1)
8	4'-MeO-Ph	Ph、NH 4'-MeO-Ph	2h (74%)	Phh.O 4'-MeO-Ph	3h (74%, 4:1)
9		2'-tolyl NH 4'-MeO-Ph	2i (73%)	2'-tolyl < +.O ⁻ 4'-MeO-Ph	3i (49%, 2:1)
10	<u>~~</u> 0	Ph`NH	2j (83%)	Ph.,+.O	3j (70%, 4:1) ^a

Table 1 (continued)

Entry	Aldehyde 1	<i>N</i> -Allyl aniline 2 (yield)		α , β -Unsaturated <i>N</i> -aryl ketonitrone 3 (yield, <i>E</i> : <i>Z</i> ratio)	
11		3'-MeO-Ph NH	2k (89%)	3'-MeO-Ph、+, O	3k (70%, >10:1) ^a
12	~~~0	Ph _{NH}	2l (75%)	Ph. ⁺ .O ⁻ II	3l (20%, 3:1)

^a Estimated yield based on integration of ¹H NMR spectra of the crude product.

The condensation of anilines and α,β -unsaturated aldehydes was carried out in diethyl ether at room temperature with MgSO₄ as the dehydrating agent.¹¹ While all the anilines that we tested condensed with equal amounts of cinnamaldehydes efficiently, slight excess of aliphatic α,β -unsaturated aldehydes (1.2 equiv) had to be used for optimal yields and product purity. Since these *N*-allylideneanilines were somewhat unstable, only simple filtration and concentration in vacuo were performed to prepare these intermediates for the subsequent transformation. Uniformly high yields were obtained for alkylation of these non-enolizable imines with alkyl and phenyl lithium reagents to give *N*-allyl anilines (2) that were mostly pure based on crude ¹H NMR spectra.¹² They were subjected to oxidation by Oxone® under the conditions reported by Busqué and Figueredo to give α,β -unsaturated N-aryl ketonitrones (3).^{8a} This modular approach allowed synthesis of α , β -unsaturated *N*-aryl ketonitrones with diverse substitutions. These include substitution of the N-aryl groups by 2'-methyl (3b), 4'-methyl (3c), 4'-chloro (3d), and 3'-methoxy (3k) groups and substitution of the ketonitrone by ethyl (3e), n-Bu (3f), and phenyl (**3g**) groups. All the α,β -unsaturated *N*-aryl ketonitrones thus prepared are β -substituted by the phenyl, 4'-methoxyphenyl, or methyl groups (those with an unsubstituted β -position could be more conveniently prepared by the Bartoli method⁵). The α - and β positions of the α , β -unsaturated *N*-aryl ketonitrones could be further substituted with the methyl group (3k and 3l). The ketonitrones thus formed showed varying degrees of stability. Most of them could be purified by column chromatography, but with slight to moderate levels of decomposition over silica gel. Thus, the yields for formation of 3 were somewhat underestimated in Table 1. Ketonitrones 3j, 3k, and 3l decomposed extensively over silica gel. Indeed, characterization of the crude material prior to purification indicated that the actual yield was much higher than obtained after chromatography.

While the C=C double bonds of **3** appeared to be all generated in the *E*-geometry when relevant, their nitrone C=N double bonds were formed as *E*,*Z*-mixtures in ratios ranging from 2:1 to >10:1. Determination of the C=N double bond geometry was straightforward when the α' -substituent was a methyl since it had been established by Bartoli that the geometry was directly correlated with the ¹H NMR chemical shift of the methyl group.⁵ A chemical shift of 2.25–2.31 ppm was associated with a C=N double bond in the *E*-configuration while a chemical shift of 1.76–1.91 ppm was indicative of a *Z*-double bond. The geometry of ketonitrones with α' -ethyl- and butyl- groups could be similarly assigned. When substituted by a phenyl group at the α' -position (**3g**), only one diastereomeric nitrone, tentatively assigned as the *E*-isomer,¹³ was observed.

In summary, α , β -unsaturated *N*-aryl ketonitrones can now be synthesized in a modular fashion that involves condensing anilines and α , β -unsaturated aldehydes to give *N*-allylideneanilines, followed by alkylation with alkyl or phenyl lithium reagents and oxidation with Oxone[®]. This procedure uses starting materials that are all commercially available and is operationally simple. It allows access to diversely substituted unsaturated ketonitrones which enable further exploration of the reactivity of these relatively unexplored species.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06. 083.

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- 13. This is based on the observation that, when $R^3 = alkyl$, the two vinyl protons of the α , β -unsaturated showed a large chemical difference in the *Z*-isomer ($\Delta \delta = 1.0-1.5$ ppm) while a smaller chemical shift difference ($\Delta \delta < 0.5$ ppm) was observed for the *E*-isomer. A chemical shift difference of $\Delta \delta = 1.5$ ppm was observed for **3f**. It was assigned as the *E*-isomer because $R^3 = Ph$.