

# One-Pot Stepwise Approach to $\beta$ -Enaminoketoesters through "Masked" 1,3-Aza-Dipoles

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**Supporting Information** 

**ABSTRACT:** *t*-BuOK-mediated rearrangement of 1,3-ketoesters with 2-(azidomethyl) aromatics in a two-step, one-pot telescoped sequence affords  $\beta$ -enaminoketoesters in moderate to good yields. A novel pathway is proposed in which the umpolung of the azide is achieved from electrophilicity to nucleophilicity via deprotopation and undergoes nucleoph



achieved from electrophilicity to nucleophilicity via deprotonation and undergoes nucleophilic attack onto the 1,3-ketoester.

 $\beta$ -Enaminoketoester, a versatile building block to construct a variety of molecules,<sup>1</sup> has been used to react with hydrazine to afford pyrazole<sup>2</sup> and also to synthesize chiral  $\beta$ -amino acid by asymmetric hydrogenation.<sup>3</sup> Tandem Blaise-acylation is known to proceed to  $\beta$ -enaminoketoesters via Reformatsky reaction with nitrile;<sup>2a</sup> 1,3-ketoester condensation with Me<sub>2</sub>NCH(OMe)<sub>2</sub> also affords the desired product.<sup>4</sup> Herein we are interested in discovering a two-step, one-pot protocol to synthesize  $\beta$ -enaminoketoesters via "masked" 1,3-aza-dipoles.

To our best knowledge, azide is a common 1,3-dipole for Huisgen cycloaddition<sup>5</sup> with alkynes and electron-deficient alkenes to yield substituted 1,2,3-triazoles<sup>6</sup> and dihydro-triazoles.<sup>7</sup> Azides show ambiphilicity under various conditions: they are nucleophilic under acidic conditions when applied in Schmidt<sup>8</sup> and Boyer reactions<sup>9</sup> and electrophilic azidation of basic enolate to approach an  $\alpha$ -amino acid<sup>10</sup> and Regitz diazo transfer.<sup>11</sup> Recently, Manetsch<sup>12</sup> reported an unusual case, in which the umpolung of the azide is achieved from electrophilicity to nucleophilic attack of the outermost nitrogen atom of benzyl azides onto an aromatic aldehyde (Scheme 1). Intrigued by Manetsch's work, herein we disclose our results in base-mediated rearrangements of 1,3-ketoesters with benzyl azides in moderate to good yields.

First, bases were screened for  $\alpha$ -C deprotonation of benzyl azide. When mild inorganic bases and amine were employed, no reaction occurred (Table 1, entries 1–3). Luckily, strong bases resulted in formation of **3a** in satisfying yields under heating conditions (Table 1, entries 4 and 5). The equivalents of base also had a significant effect on product yield (Table 1, entries 6–9). The reaction could proceed successfully in DMF (Table 1, entry 5), but other solvents including DMSO, THF, toluene, EtOH, and CH<sub>2</sub>Cl<sub>2</sub> gave low yields (Table 1, entries 10–14).

With the optimized reaction conditions, the two-step, one-pot telescoped sequence works well using both benzyl chloride and bromide (Table 2, 3b-3f). Alkyl ketoesters (including primary, secondary, and tertiary substituents) afforded (*E*)- $\beta$ -enamino-ketoesters as sole isomers in good yields (Table 2, 3b-3k). The sole *E* isomer of 3d was further confirmed by X-ray diffraction

Scheme 1. Rearrangements of 1,3-Ketoesters with Benzyl Azide Compared with Aldehyde Amidation with Benzyl Azide

Manetsch's work



analysis (Figure 1 and Supporting Information). Mild electrondeficient (Table 2, 3h), electron-donating (Table 2, 3g, 3i), and halogen-substituted (Table 2, 3j, 3k) benzyl azides were tolerated, giving rise to the desired products in good yields. However, benzyl azides with strong electron-withdrawing substituents did not work (p-NO<sub>2</sub>, p-CO<sub>2</sub>Et). On the other hand, aliphatic azides (n-hexyl azide and cyclohexyl azide) decomposed under the condition. 1,3-Ketoesters bearing benzoyl groups were also employed (Table 2, 3I-3p). Aromatic ketoesters were found to transform to 3 (E/Z mixtures) more slowly (36 h), during which trace amounts of 2-benzoyl-3-phenyl acrylates were detected (ESI-MS) as byproducts.

On the basis of our experiment results, a putative mechanism is proposed (Scheme 2). Deprotonation of benzyl azide first generates a highly reactive species 4, the outermost nitrogen atom of which undergoes nucleophilic attack onto the carbonyl carbon of ketone 2. Intramolecular proton shift gives the nucleophilic carbanion 6 *in situ*, followed by an intramolecular Mannich reaction via a six-membered chairlike transition state to yield triazenide 7. Then, proton shift affords an electronintensive oxide 8, followed by elimination of molecular nitrogen

**Received:** July 3, 2014 **Published:** July 23, 2014 Table 1. Optimization of 1,3-Ketoesters Rearrangement with Benzyl Azide $^{a}$ 

2 2 1a	Br solvent 70 °C overnight 2	N <sub>3</sub>	O 2a Se, solvent 12 h	O O O O O O O Pr O Ph 3a (E)
entry	base (equiv)	solvent	<i>t</i> (°C)	yield $(\%)^b$
1	$Cs_2CO_3(2)$	DMF	70	nr
2	$K_{2}CO_{3}(2)$	DMF	70	nr
3	$Et_3N(2)$	DMF	70	nr
4	KOH (2)	DMF	70	81
5	<i>t</i> -BuOK (2)	DMF	70	88
6	t-BuOK (4)	DMF	70	85
7	<i>t</i> -BuOK (1)	DMF	70	68
8	<i>t</i> -BuOK (0.5)	DMF	70	trace
9	<i>t</i> -BuOK (0.1)	DMF	70	nr
$10^{c}$	t-BuOK (2)	DMSO	70	trace
11	t-BuOK (2)	THF	70	7
12	t-BuOK (2)	toluene	70	nr
13	t-BuOK (2)	EtOH	70	nr
14	t-BuOK (2)	DCM	70	26
15	t-BuOK (2)	DMF	rt	14
16	t-BuOK (2)	DMF	50	35
17	t-BuOK (2)	DMF	90	77

<sup>*a*</sup>Reaction conditions: **1a** (1 mmol) and sodium azide (1.1 mmol) were dissolved in solvent (3 mL) and stirred at 70 °C overnight, followed by treatment with base and **2a** (0.5 mmol), and stirring continued at 70 °C (except for entries 15–17) in a sealed tube for 12 h. The equivalent of base is based on **2a**. <sup>*b*</sup>Isolated yield. nr = no reaction. <sup>c</sup>DMSO is not versatile for all substrates and works only for particular substrates; see Table 2.

leading to  $\beta$ -amino ketoesters 9. One equivalent of ammonia gas,<sup>13</sup> which was detected by wet litmus paper, is lost under heating condition, leading to 2-acyl-substituted acrylate derivative 10. [3 + 2] Cycloaddition of 10 with a second equivalent of azide yields a "masked" 1,3-aza-dipole, namely, substituted triazole 11, which is unstable and releases N<sub>2</sub><sup>14</sup> in situ to generate a zwitterionic species 12. Finally, 1,2-proton shift and imineenamine tautomerization affords  $\beta$ -enaminoketoesters 3. The sole *E* selectivity of 3a-3k could be explained by intramolecular H-bonding between the imine and enol group<sup>4d,e</sup> in 13, while the pool *Z*/*E* selectivity of 3l-3p could possibly be explained by steric hindrance between benzoyl substituents and imine, leading to rotation of ketoester's  $\alpha$ -C- $\beta$ -C  $\sigma$  bond to a partial *Z* isomer during the tautomerization process.

To further illustrate the envisioned mechanism, we employed a mild sterically hindered azide 3-(azidomethyl)-1,1'-biphenyl<sup>15</sup> and the more bulky 1-(azidomethyl)naphthalene for the rearrangement but isolated only 2-acetyl-3-aromatic acrylates (Scheme 3, **10q**, **10r**) as the sole product with no  $\beta$ enaminoketoesters detected (Scheme 3).

This could be explained by prohibition of [3 + 2] cycloaddition because of steric hindrance at the  $\beta$ -position of substituted acrylates **10**. On the other hand, **10b** obtained from an aldol condensation protocol<sup>16</sup> could also react with the benzyl azide to afford  $\beta$ -enaminoketoester **3b**, which illustrates that **10** is likely a key intermediate in the proposed pathway of *t*-BuOK-mediated rearrangement of 1,3-ketoesters with benzyl azides. To further exclude the possibility that the deprotonated benzylic azide loses molecular nitrogen to form benzylideneamide *in situ* and undergoes Mannich reaction by enolate of the 1,3-ketoester, a



Table 2. t-BuOK-Mediated 1,3-Ketoester Rearrangements with Benzyl Azides  $^a$ 

"Reaction procedure: **1a** (1 mmol) and sodium azide (1.1 mmol) were dissolved in DMF (3 mL) and stirred at 70 °C overnight, followed by treatment with *t*-BuOK (1 mmol) and **2a** (0.5 mmol), and stirrring continued at 70 °C in a sealed tube for 12-36 h. <sup>b</sup>In DMSO (3 mL).



Figure 1. X-ray crystal structure of 3d.

control experiment was conducted wherein the azide was stirred with *t*-BuOK at 70  $^{\circ}$ C for 10 min, and then 1,3-ketoester was added to the mixture. Interestingly, most of the azide decomposed, with the product formed in trace amounts.

In conclusion, 1,3-ketoesters have been used to rearrange with benzyl azides to afford  $\beta$ -enaminoketoesters in moderate to good

#### Scheme 2. Possible Reaction Mechanism



Scheme 3. Isolated Intermediates 10, Rearrangement of 10 with Benzyl Azide, and Related Control Experiment



yields. The mild, straightforward experimental condition should prove valuable in both academic and industrial research settings.

# ASSOCIATED CONTENT

# **Supporting Information**

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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