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## COMMUNICATION

# A Straightforward and Versatile Protocol for the Direct Conversion of Benzylic Azides to Ketones and Aldehydes

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The synthesis of carbonyl compounds from benzylic azides through benzylideneamides is described for the first time. NaHmediated activation of benzyl azides allows a rapid waterpromoted oxidation under a facile protocol with good yields.

The chemistry of organic azides is very well-known. Books<sup>1</sup> and reviews<sup>2</sup> have compiled the role of these valuable nitrogen compounds as mediators between chemistry, medicine, biology and materials science. As synthetic intermediates, organic azides can be coupled to other substrates (e.g. 1,3-dipolar cycloaddition)<sup>3</sup> or directly converted to other functional groups, such by reduction (e.g. Staudinger reaction)<sup>4</sup> or by an oxidation process. Regarding the latter, there are reports on obtaining nitro compounds<sup>5</sup> (oxidation of the -N<sub>3</sub> moiety) as well as synthesizing nitriles<sup>6</sup> (oxidation of benzylic carbon). In this context, synthetic strategies to achieve carbonyls from azido groups (Scheme 1)<sup>7</sup> (an inverse reaction as proposed by Ghorai)<sup>8</sup> are still challenging and attractive for organic chemists. Unfortunately, all such strategies developed to date [Eq. (a)-(f)] suffer from serious drawbacks, including the use of metals as reagents that are very expensive and/or unconventional and require the use of peroxides, as well as cumbersome experimental procedures or high temperatures that are particularly disadvantageous for large-scale reactions.

Synthetic strategies involving the acidic hydrolysis of enamines [Scheme 2, Eq. (g)] or imines [Eq. (h)] generated *in situ* from azide compounds have been reported in literature. Hendrickson (1977)<sup>9a</sup> and Hassner (1979)<sup>9b</sup> published the direct conversion of vinyl azides to carbonyls via enamines in good yields. Although the thermal, photolytic and acidic decomposition of organic azides to imines has been studied extensively<sup>10,12g</sup> their applications for obtaining carbonylic compounds<sup>11</sup> are rather limited. The high temperatures (ca. 300°C) required for a thermal process in the synthesis of alde–



Scheme 1. Recent advances in the synthesis of carbonyl derivatives from azide compounds.

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Electronic Supplementary Information (ESI) available: Characterization data and copies of <sup>1</sup>H-NMR/<sup>13</sup>C-NMR of all compounds. See DOI: 10.1039/x0xx00000x



Scheme 2. Acidic hydrolysis of enamines (efficient) or imines (inefficient) generated *in situ* from azide derivatives representing synthetic strategies for the attainment of carbonyls.

hydes from alkylic azides<sup>12a</sup> (inefficient for benzylic azides)<sup>12b</sup> preclude the use of this type of reaction for most substrates. In contrast, a photolytic process using primary alkyl azides<sup>12c-f</sup> occurs at or below room temperature. However, its use is limited by very low yields (18–50%) from a complex reaction mixture. Finally, trace amounts of carbonyls have been observed under strong acid conditions.<sup>[12g-i]</sup> The evident inefficiency of all these methods as synthetic strategies to afford carbonyls from azides via imines has led to complete disinterest and abandonment of their use, a fact that has been demonstrated by the absence of studies in contemporary literature.<sup>[13]</sup>

Previously Manetsch<sup>[14a]</sup> and Wu/Pan<sup>[14b]</sup> demonstrated the <sup>t</sup>BuOK-promoted attainment of PhCH=N<sup>-</sup> (benzylideneamide) from PhCH<sub>2</sub>N<sub>3</sub> as well as its *inefficient* use for coupling the latter with carbonyl compounds. We herein describe the utility of benzylideneamides for directly converting benzyl azides to carbonyl derivatives with good yields.

During one of our current research programs, focused on the development of novel methodologies for the construction of 1,2,3-triazole moieties through base-promoted azide-ketone cycloadditions<sup>[15]</sup> we observed that when NaH was subjected to our study, benzaldehyde was isolated as by-product along with the corresponding triazole. Intrigued by this outcome, we decided to do follow-up investigation this fact in greater detail.

Firstly, in absence of ketones (in order to avoid the formation of the corresponding triazole) good yields were observed at room temperature with a reaction time of 4 h. Secondly, the effects of solvents and bases on compound **1a** were observed in optimization studies (Table 1). The best performance was found for NaH (entry 9) in dimethyl sulfoxide using 2.0 equivalents of the base. The optimized conditions were then used to study the direct conversion of a variety of azides<sup>†</sup> to aldehydes (Scheme 3).<sup>‡</sup> In order to evaluate the scope of our protocol, both benzylic and aliphatic azides were subjected to the optimized reaction conditions. Unfortunately, aliphatic compounds (**4n** and **4o**) did not react to

Table 1. Optimization of reaction conditions:<sup>[a]</sup> Effect of solvent and base

	N <sub>3</sub> 1a	1) Solvent, 4 h 2) H <sub>2</sub> O (work-up) 4a	
Entry	Solvent	Base <sup>[b]</sup>	Yield (%) <sup>[c]</sup>
1	DMF anh.	NaH	70
2	DMF anh.	K <sub>2</sub> CO <sub>3</sub>	NR <sup>[e]</sup>
3 <sup>[d]</sup>	DMF anh.	K <sub>2</sub> CO <sub>3</sub>	NR <sup>[e]</sup>
4	DMF anh.	<sup>t</sup> BuOK	60
5	DMF anh.	КОН	Trace <sup>[e]</sup>
6 <sup>[d]</sup>	DMF anh.	КОН	45
7	MeCN anh.	NaH	35
8	DMSO anh.	<sup>t</sup> BuOK	72
9	DMSO anh.	NaH	80
10	DMSO anh.	NaH (1.5 eq)	74 <sup>[f]</sup>
11	DMSO anh.	NaH (1.0 eq)	70 <sup>[f]</sup>

<sup>[a]</sup> Unless otherwise stated, reactions were run at room temperature for 8 h.

<sup>[b]</sup> Unless otherwise stated, reactions were performed using 2.0 eq.

<sup>[c]</sup> Yields refer to chromatographically pure isolated compounds.

<sup>[d]</sup> These experiments were carried out at 60 °C.

<sup>[e]</sup> Starting material was recovered.

<sup>[1]</sup> Along with the corresponding starting material (~15% recovered)



Scheme 3. Direct conversion of primary azides (1) to aldehydes (4) under optimized conditions. Reaction conditions: NaH (0.2 mmol) was added to a solution of compound 1 (0.1 mmol) in DMSO anh. Then, water was added in excess.

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Scheme 4. Direct conversion of secondary azides (5) to ketones (6) under optimized condicions. Reaction conditions: NaH (0.2 mmol) was added to a solution of compound 5 (0.1 mmol) in DMSO anh. Then, water was added in excess

such conditions remaining intact in the flask even under thermal conditions (60 ºC). Therefore, only benzylic azides were considered for the present study. An effective approach to the aldehyde derivatives was carried out with heterocycles (4j), strongly (4c, 4d, 4e, 4g and 4i) and weakly (4f) activated rings as well as weakly deactivated (4h) rings. The exception was strongly deactivated rings (4k, 4l and 4m).

Encouraged by these outcomes, we decided to investigate another possibility: the synthesis of ketones using secondary azido groups. We therefore submitted the (1-azidoethyl)benzene  $[PhCH(N_3)CH_3]$  to the current protocol achieving the synthesis of the corresponding acetophenone (6a, Scheme 4) with good yields (85%). Therefore, a series of compounds containing secondary azides' were studied under the same reaction conditions.

At this stage we found the behavior similar to that observed for primary azides including the lack of reaction for aliphatic (6k) and strongly deactivated aromatic rings (6m). Two interesting exceptions were N=C- [a strongly deactivating derivative (6b)] and F-substituted [a weakly deactivating derivative (6I)].

Finally, in order to demonstrate the scalability of such protocol, acetophenone (6a) was efficiently obtained (80%) from 10.0 g of the corresponding starting material [PhCH(N<sub>3</sub>)CH<sub>3</sub>]. The use of ice bath was necessary due to the exothermic reaction observed along with the intense bubbling  $(N_2\uparrow)$  during the addition (in five portions) of the hydride.

According to these results, a plausible mechanism is proposed in Scheme 5. The generation of benzylideneamide (III) by a basepromoted deprotonation of the benzyl azide (I) is supported by previous studies (Manetsch<sup>[14a]</sup> and Wu/Pan<sup>[14b]</sup>). We propose that this was followed by a rapid hydrolysis under basic conditions leading to the corresponding carbonyl group (VI).



Scheme 5. Proposed plausible mechanism for direct conversion of benzyl azido groups to carbonyl derivatives.

#### Conclusions

In summary, we report that the benzyl azido group is directly converted to carbonyls in good yields through a rapid hydrolysis (basic conditions) of benzylideneamides generated readily/efficiently in situ. We are convinced that this synthesis is the most versatile reported so far as its scope includes both primary azides (affording aldehydes) and secondary azides (affording ketones) reacted with conventional reagents under a very simple procedure.

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#### Notes and references

<sup>†</sup> Azide compounds (starting materials) were obtained from the corresponding alcohols<sup>[16]</sup>, halides<sup>[17]</sup> or tosylates<sup>[18]</sup> according to synthetic protocols described in literature.

‡ General experimental procedure for the direct conversion of azides to carbonyls: NaH (0.4 mmol, 60 % dispersion in mineral oil) was added to a solution of the azide derivative (0.2 mmol) in anhydrous dimethyl sulfoxide (ca. 2.0 mL/mmol). The solution was stirred at room temperature for 4 h under an inert atmosphere. Brine (ca. 20.0 mL) was added to the reaction stirring vigorously for 15 min. Then, the mixture was washed with ethyl acetate (3 x 8 mL). The organic layer was dried  $(Na_2SO_4)$ , and the solvent was evaporated under reduced pressure. The crude extract was purified

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by flash column chromatography to afford the corresponding carbonyl derivative.

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### Graphical and textual abstract for the contents pages



We report that the benzyl azido group is directly converted to carbonyls in good yields through a rapid hydrolysis (basic conditions) of benzylideneamides generated readily/efficiently *in situ* under a very simple procedure involving conventional reagents.