ChemPubSoc Europe

DOI: 10.1002/ejoc.201501374

EurJOC European Journal of Organic Chemistry

Communication

Tertiary Azidation

An Efficient Tertiary Azidation of 1,3-Dicarbonyl Compounds in Water Catalyzed by Tetrabutylammonium Iodide

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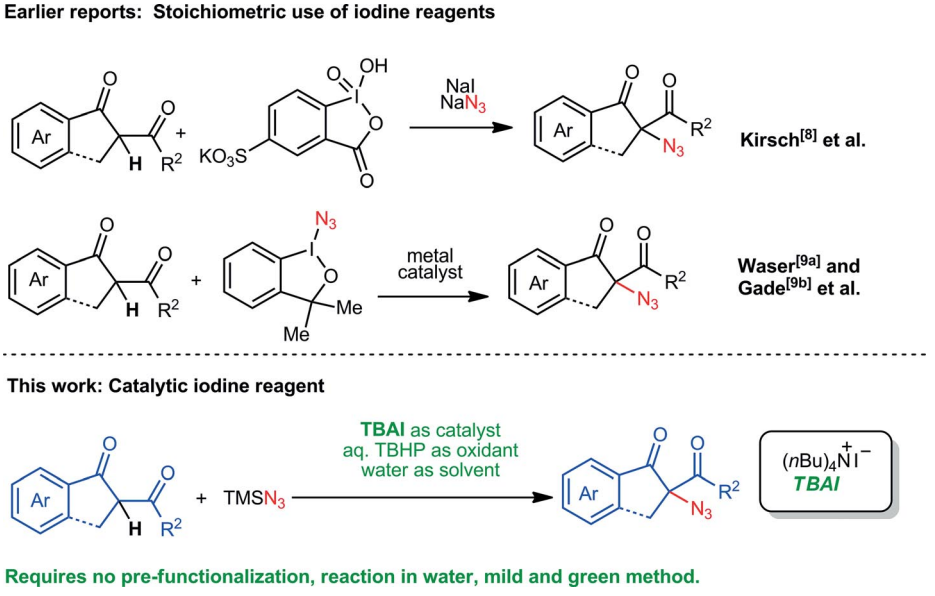
Abstract: An efficient azidation of 1,3-dicarbonyl compounds led to tertiary azides in the presence of tetrabutylammonium iodide (TBAI). TBAI is used as a pre-catalyst along with aq. *tert*-butyl hydroperoxide (TBHP) as an oxidant in aqueous medium. This operationally simple, practical, mild and green method provides an opportunity to synthesize a variety of azidated β-keto esters, amides, and ketones in good yields.

Introduction

Azidation has emerged as one of the methods for incorporating nitrogen in to organic molecules,[1] which also provides an opportunity for late-stage modification of complex molecules like biomolecules, drug candidates, polymers etc.[1] The wide applicability of click reactions and the stability of azides in water have provided additional impetus for exploring novel methods of synthesizing a variety of azides and their reactions.[1,2] The traditional methods of synthesizing alkyl azides by S_N2 displacement cannot be employed for synthesizing secondary and tertiary azides.[3] Azidation of 1,3-dicarbonyl compounds is an important reaction as the azides formed in this reaction can be easily transformed into their α-amino derivatives.[4] But, the azidation of 1,3-dicarbonyl compounds is challenging, as both azides and 1,3-dicarbonyl compounds are nucleophilic in nature.[5] To address this issue, electrophilic azide sources such as sulfonyl azides have been developed,[6] which can be used for the azidation of strong nucleophiles. However, these azidation reactions with 1,3-dicarbonyl compounds led to the competing diazo transfer reactions and deacylative rearrangements.[6] To circumvent this problem, Moriarty and others employed in situ generated electrophilic 1,3-dicarbonyl compounds in the presence of iodosobenzene and a Lewis acid.[7] Later, Kirsch's group



Scheme 1. Development of the reaction.

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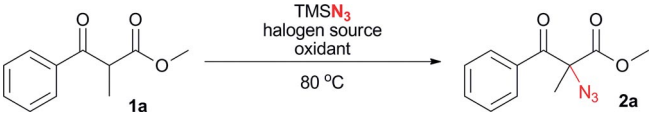
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501374.

reported azidation of 1,3-dicarbonyl compounds by using a stoichiometric amount of molecular iodine or 2-iodoxybenzoic acid (IBX), NaI, and NaN_3 (Scheme 1).[8] Gade and Waser reported azidation of β-keto esters and silyl enol ethers with a benziodoxole reagent and a Lewis acid (Scheme 1).[9] Ibrahim et al. reported the α-azidation of 1,3-dicarbonyl compounds by using a stoichiometric amount of diacetoxy iodobenzene and tetrabutylammonium azide.[10] The hypervalent iodine reagents are environmentally benign, and hence the utility of these reagents is very attractive. However, most of these methods use large amounts of hypervalent iodine reagents[11] and a few methods also require metal catalysts, such as $Zn(OTf)_2$, Fe-complexes etc., for activating the 1,3-dicarbonyls. Therefore, the development of a mild reaction that is more atom-efficient and simple with low catalyst loading and that produces less waste is desirable. To address these issues, in his seminal work, Ishihara developed a tetraalkylammonium iodide (catalytic) with H_2O_2 or TBHP system for an in situ generation of hypoiodite/iodate species that mimics the hypervalent iodine mediated reactions to carry out enantioselective oxidative cycloetherification of ketophenols.[7,12] In pursuit of our efforts directed toward developing iodine-based catalytic systems,[13] herein we report our recent findings on TBAI/TBHP-catalyzed azidation of 1,3-dicarbonyl compounds to obtain tertiary azidated 1,3-dicarbonyl compounds in aqueous medium.

Results and Discussion

We started the optimization study with acyclic β-keto ester, methyl 2-methyl-3-oxo-3-phenylpropanoate (**1a**), $TMSN_3$ as azide source, TBAI as a catalyst (10 mol-%) and TBHP as an oxidant in 1,2-dichloroethane (DCE). This reaction led to the azidated product **2a** in 51 % yield (determined by NMR spectroscopy, Table 1, entry 1). The solvent screening studies revealed that EtOAc is the most suitable solvent (entry 2) and most of the other solvents are useful (entries 3–8). Further, using water as a solvent, we were pleased to note that the reaction was facile and furnished the product **2a** in a quantitative yield (entry 9). As water is a desirable solvent for chemical reactions for reasons of safety, cost, and environmental concerns,[2a] we have carried out all further studies in water. Other iodine sources, such as *N*-iodosuccinimide (NIS), molecular iodine, and KI, were not found to be suitable (entries 10–12). While other halogen sources, such as tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC), and *N*-chlorosuccinimide (NCS) as catalysts did not furnish the corresponding product (entries 13–15). Among the oxidants, aq. H_2O_2 gave the product **2a** in 62 % (Table 1, entry 16), whereas other oxidants produced either low yield or no product (entries 17–19). The use of sodium azide was not successful under the given reaction conditions (entry 20). Lowering the amounts of TBAI and $TMSN_3$ to 5 mol-% and 1.2 equiv., respectively, resulted in the formation of the product **2a** in slightly lower yields (92 and 90 %, respectively, entries 21 and 22). Lowering the amount of TBHP to 1 equiv. decreased the yield (88 %, entry 23). In the absence of either TBAI or TBHP, the reaction did not proceed (entries 24 and 25) indicating that both TBAI and TBHP are essential for the reaction.

Table 1. Screening studies.[a]

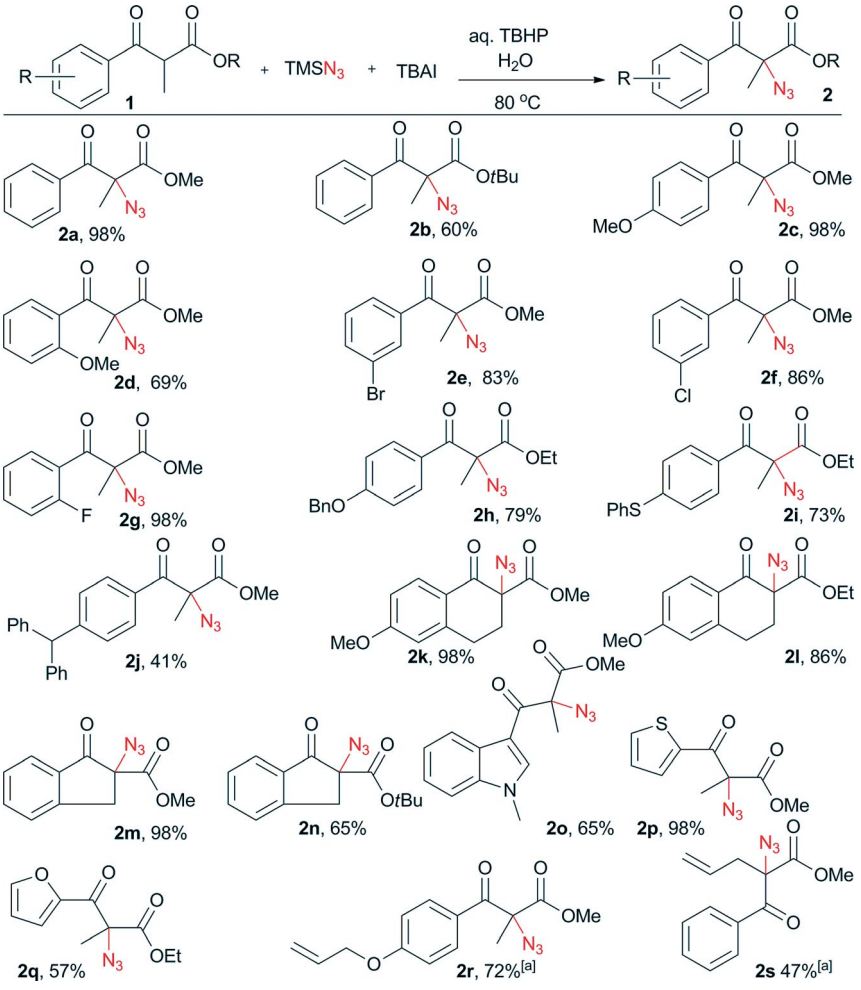


Entry	Halogen source (10 mol-%)	Oxidant (2 equiv.)	Solvent (2 mL)	Yield [%][b]
1	TBAI	TBHP	DCE	51
2	**TBAI**	TBHP	**EtOAc**	**98**
3	TBAI	TBHP	toluene	94
4	TBAI	TBHP	1,4-dioxane	90
5	TBAI	TBHP	CH_3CN	93
6	TBAI	TBHP	MeOH	84
7	TBAI	TBHP	DMSO	87
8	TBAI	TBHP	DMF	62
9	**TBAI**	**TBHP**	**water**	**98**
10	NIS	TBHP	water	traces
11	I_2	TBHP	water	10
12	KI	TBHP	water	22
13	TBAB	TBHP	water	ND
14	TBAC	TBHP	water	ND
15	NCS	TBHP	water	traces
16	TBAI	aq. H_2O_2 (30 %)	water	62
17	TBAI	DTBP	water	ND
18	TBAI	BPO	water	21
19	TBAI	O_2	water	ND
20[c]	TBAI	TBHP	water	ND
21[d]	TBAI	TBHP	water	92
22[e]	TBAI	TBHP	water	90
23[f]	TBAI	TBHP	water	88
24	none	TBHP	water	ND
25	TBAI	none	water	ND

[a] Reaction conditions: **1a** (0.26 mmol), $TMSN_3$ (0.52 mmol), aq. TBHP (2 equiv., 70 % in water) at 80 °C. [b] Yield determined by ^1H NMR spectroscopy (by using terephthalaldehyde as an internal standard). [c] NaN_3 (2 equiv.) was used instead of $TMSN_3$. [d] TBAI (5 mol-%) was used. [e] 1.2 equiv. of $TMSN_3$ was used. [f] 1 equiv. of aq. TBHP was used. ND = not determined, DTBP = di-*tert*-butylperoxide, BPO = benzoyl peroxide.

Finally, the conditions using 10 mol-% of TBAI, 2 equiv. of TBHP and 2 equiv. of $TMSN_3$ in water (entry 9) were established as the optimal conditions. Next, the substrate scope and generality of the reaction was explored under the optimized conditions. Employing methyl and *tert*-butyl β-keto esters under the optimal reaction conditions afforded the azidated products **2a** and **2b** in excellent to good yields (98 and 60 %, respectively, Scheme 2). Substrates with electron-releasing and electron-withdrawing groups on the phenyl ring of β-keto esters gave the azidated products **2c**, **2d**, **2e**, **2f**, and **2g** in moderate to excellent yields (98, 69, 83, 86, and 98 %, respectively, Scheme 2).

An excellent chemoselective reaction was observed in the presence of oxidizable functional groups on the phenyl ring of β-keto esters. Thus, an *O*-benzyl group in the phenyl ring survived the reaction conditions to afford the azidated product **2h** in 79 % yield. The easily oxidizable sulfenyl group was intact and afforded azidated product **2i** in 73 % yield. Similarly, a benzhydryl group was found to be moderately tolerated in the reaction conditions and the corresponding azidated product **2j** was obtained in moderate yield (41 %). 1-Tetralone and 1-indanone derived cyclic β-keto esters, are more reactive than acyclic



Scheme 2. Substrate scope for β-keto esters. Reaction conditions: **1** (0.26 mmol), $TMSN_3$ (0.52 mmol), aq. TBHP (2 equiv.), TBAI (10 mol-%), H_2O (2 mL), at 80 °C, 3–12 h. Yields given are of the isolated products. [a] Reaction in EtOAc (2 mL).

esters[9a] and were found to give the corresponding products in excellent yields. Notably, the similar reaction of 1-tetralone with hypervalent iodine reagent such as azidobenziodoxole[9a] led to complete aromatization, whereas under the present reaction conditions, we obtained the corresponding tertiary azides (**2k** and **2l**) in excellent yields.

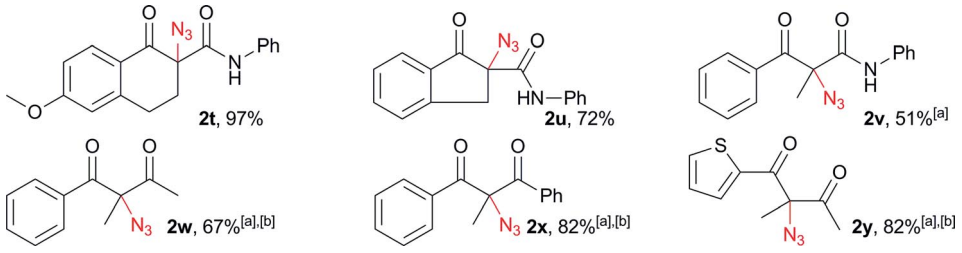
Thus, methyl, ethyl, and *tert*-butyl ester derivatives underwent a smooth reaction to give the azidated products **2k**, **2l**, **2m**, and **2n** in good to excellent yields (98, 86, 98, and 65 %, respectively, Scheme 2). The azidation of heterocyclic compounds such as, indole, thiophene, and furan derived β-keto esters was facile and afforded the azidated products **2o**, **2p**, and **2q** in moderate to excellent yields (65, 98, and 57 %, Scheme 2).

Substitutions such as an *O*-allyl group on the phenyl ring and aliphatic β-keto esters failed to provide the azidated products under the optimal reaction conditions. However, by changing the solvent from water to EtOAc, azidated product **2r** is obtained in 72 % yield. Similarly, a β-keto ester with an allyl group at the α-position furnished the expected product **2s** by performing the reaction in EtOAc in moderate yield (47 %).[14]

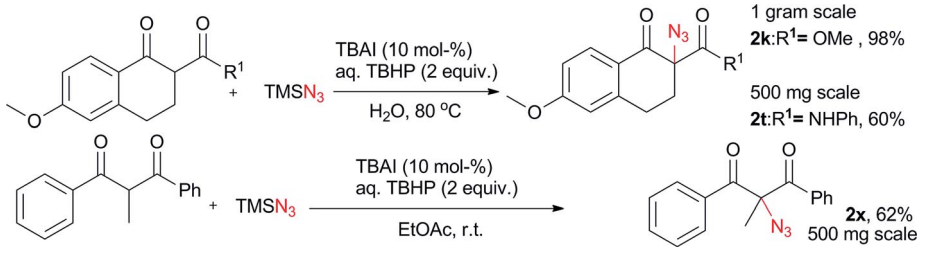
After successful azidation of β-keto esters, it was found that the same catalytic system is useful for azidation of β-keto amides (Scheme 3). Thus, β-keto amides of 1-tetralone and 1-indanone underwent a smooth reaction to furnish the corresponding azidated products **2t** and **2u** in 97 and 72 % yields, respectively. The azidation of acyclic amide in EtOAc (as a solvent) afforded the azidated product **2v** in 51 % yield. The azidation of 1,3-diketones, which are highly reactive compared to esters and amides, was not successful under optimal reaction conditions. Nevertheless, the reaction in ethyl acetate as solvent instead of water proceeded well to yield the azidated products **2w**, **2x**, and **2y** in moderate to good yields (67, 82, and 82 %, respectively).

To demonstrate the utility of the azidation reaction, a few experiments were performed on a larger scale as presented in Scheme 4. Employing 5.2 mmol (1 g) of methyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate under the standard reaction conditions the azidated product **2k** was obtained in almost quantitative yield (98 %). Similarly, the azidation reaction of β-ketoamides and 1,3-diketones on a 500 mg scale furnished the products **2t** and **2x** in good yields (60 and 62 %).

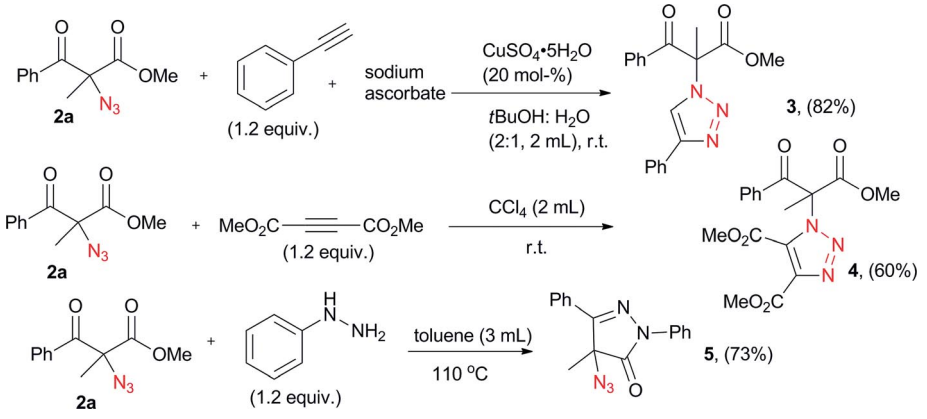
The utility of tertiary azidated products was further emphasized by subjecting **2a** to "click" chemistry conditions to obtain



Scheme 3. Substrate scope for β-keto amides and 1,3-diketones. Reaction conditions: **1** (0.26 mmol), **2**, $TMSN_3$ (0.52 mmol), aq. TBHP (2 equiv.), TBAI (10 mol-%), H_2O (2 mL), at 80 °C, 3–12 h. Yields given are of the isolated products. [a] Reaction in EtOAc (2 mL). [b] Reaction at room temp.

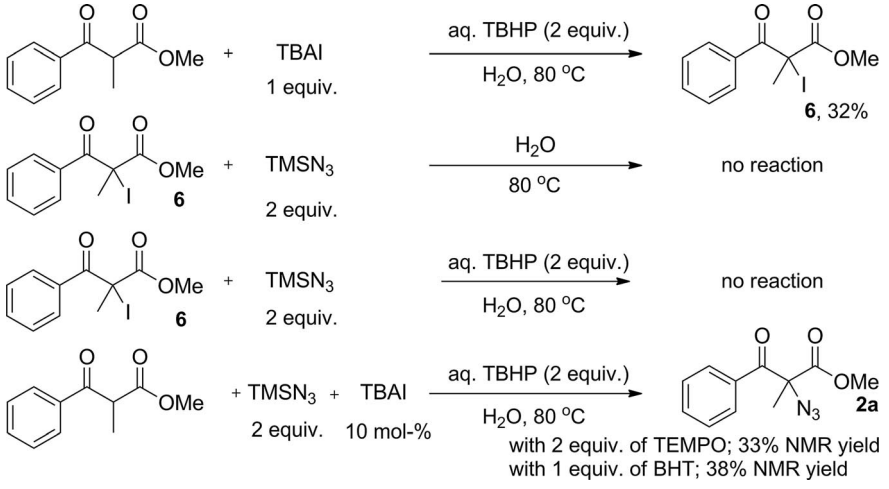


Scheme 4. Larger-scale reactions.



Scheme 5. Synthetic transformations.

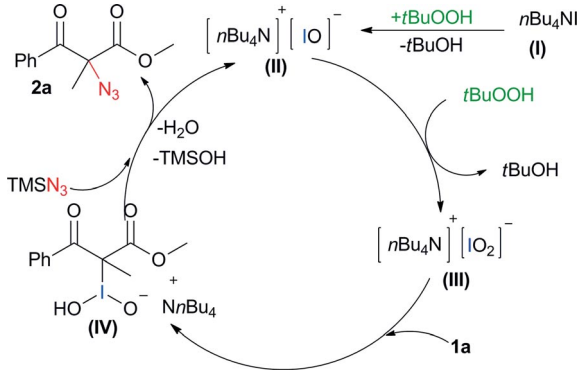
the triazoles **3** and **4** in good yields (82 and 60 %, Scheme 5). The azido-β-keto ester **2a** on further reaction with phenyl hydrazine furnished pyrazolone derivative **5** in 73 % yield, which is analogous to drug candidates such as ampyrone and metamizole. These compounds are otherwise difficult to access and are synthesized using long synthetic sequences.[15]



Scheme 6. Control experiments.

For probing the reaction mechanism, a few control experiments were performed (Scheme 6). Using a stoichiometric amount of TBAI in the absence of $TMSN_3$, which furnished α-iodo-β-keto ester **6** in 32 % yield, suggested an iodo derivative as a possible intermediate. However, employing pre-made α-iodo-β-keto ester **6**, with $TMSN_3$ failed to furnish the expected product in either the presence or the absence of aq. TBHP. Reaction in the presence of a radical inhibitor such as butylated hydroxytoluene (BHT) or a radical quencher such as TEMPO under the standard reaction conditions gave the azidated product **2a** in lower yields of 33 and 38 %, respectively, suggesting a radical pathway.

Based on these control experiments and the literature precedence,[12a,12b] a plausible mechanism is proposed in Scheme 7. An in situ reaction of TBAI and TBHP generates hypoiodite (**III**), which upon reaction with active methylene compounds forms the intermediate (**IV**). Further, the intermediate (**IV**) reacts with $TMSN_3$ to furnish the azidated product **(2a)**. We believe that, the hypernucleofugal ability of the intermediate (**IV**) formed during the reaction drives the reaction for displacement by azide.[16,17]



Scheme 7. Plausible mechanism.

Conclusions

In conclusion, we have developed an operationally simple, mild, efficient, and environmentally benign method for azidation of α-substituted β-keto esters, amides, and ketones leading to the formation of tertiary azides in high yields. This oxidative azidation is catalyzed by tetrabutylammonium iodide and the reaction has been performed using aq. TBHP as an oxidant. We propose to use chiral ammonium iodides as catalysts to introduce chirality in the molecule and such work is under progress in our laboratory.

Experimental Section

CAUTION! It is highly important to take sufficient precautions while using azides.

Typical Experimental Procedure: TBAI (0.1 equiv., 10 mg, 0.026 mmol) and aq. TBHP (70 % solution in water, 2 equiv., 0.52 mmol, 0.07 mL) were added to a mixture of 1,3-dicarbonyl compound (0.26 mmol) and $TMSN_3$ (2 equiv., 0.52 mmol) in ethyl acetate or water (2 mL) under open air. The reaction vessel was capped and the mixture was allowed to stir at 80 °C (for 1,3-diketones at room temperature) for 3–12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched using saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography using hexane/EtOAc to get the pure product.

Acknowledgments

This work was supported by SERB (No.SB/S1/OC-56/2013), New Delhi, the Indian Institute of Science, and RL Fine Chem. We thank Dr. A. R. Ramesha (RL Fine Chem) for useful discussions. J. D. thanks Council of Scientific and Industrial Research (CSIR), New Delhi, for a fellowship.

Keywords: Azides · Iodine · Keto esters · 1,3-Dicarbonyl compounds · Synthetic methods

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[17] At this point, it is not very clear that the reaction is proceeding through an ionic mechanism, a possible radical mechanism has been proposed, see Scheme S1 in the Supporting Information.

Received: October 29, 2015
Published Online: December 15, 2015