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Practical Azidation of 1,3-Dicarbonyls

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Abstract: An operationally simple, direct azidation of 1,3-dicarbonyl compounds has been developed. The reaction proceeds readily under ambient conditions using sodium azide and an iodine-based oxidant such as I_2 or 2-iodoxybenzoic acid (IBX)-SO_3K/NaI. In particular, the latter method, as a new and well-balanced oxidizing agent, shows excellent functional group tolerance and substrate scope and thus allows access to a variety of tertiary 2-azido and 2,2-bisazido 1,3-dicarbonyl compounds that would be more difficult to access by using traditional methods. Because the azide-containing products easily undergo 1,3-dipolar cycloaddition with alkynes, our report represents a novel route to analogues of sensitive complex molecules.

Keywords: azides · chemoselectivity · click chemistry · hypervalent compounds · oxidation

Introduction

The chemoselective functionalization of molecules by the use of click chemistry is a powerful tool for a diverse range of important tasks, from dendrimer design[1] to drug discovery[2] and bioorthogonal labeling of biomolecules.[3] Because of this, easy-to-perform click chemistry that is insensitive to oxygen and water, and that uses readily available reagents, is of tremendous value and is a field of ongoing interest.[4] Over the last decade, major breakthroughs in this area have been made in the realm of Huisgen's 1,3-dipolar cycloaddition[5] of alkynes and azides, yielding triazoles.[6] In particular, the inert nature of these functional groups towards biological molecules and towards living systems have led to the development of a remarkable range of applications based on this reaction.[7] Given the high chemoselectivity of the azide–alkyne coupling, click approaches that aim to react densely functionalized molecules (e.g., natural secondary metabolites) for drug discovery issues and for testing biological functions are only hampered by the fact that either a terminal alkyne or an azide moiety must be installed into the targeted molecule. It is somewhat surprising, therefore, that methods for the direct azidation of complex starting materials are sparse.

Several common methods for the construction of alkyl azides[8] are based on classical nucleophilic substitution reactions (such as the Mitsunobu reaction with alcohols[9] or substitution with alkyl halides).[10] Unlike the click reaction itself, however, when these methods are applied to multiply functionalized molecules, often, protecting group strategies or lengthy synthetic sequences are necessary due to chemo- and regioselectivity issues during the azidation (or the prerequisite halogenation to access alkyl halides). These difficulties prompted chemists to develop other modes of azidation, such as the conversion of primary amines into azides through diazo transfer, which has become particularly attractive for functionalizing natural products.[11] Some oxidative methods have been reported that employ azide radicals to introduce the azide functionality by substitution of active hydrogen atoms.[12] For example, Magnus and others have studied the azidation of enolic bonds and amines with hypervalent iodine(III) compounds and azidotrimethylsilane in great detail.[13] In a series of works, Bols et al. have demonstrated that iodine azide can be used not only for the addition to olefins, as pioneered by Hassner et al.,[14,15] but also for the azidation of aldehydes, benzal acetals, and benzyl ethers.[16] However, these methods (the mechanisms of which have been assumed to occur through azide radicals) are somewhat lacking in practice; they were mostly utilized to azidate rather simple molecules that do not bear other functional groups. We feel that a complementary method for the azidation of complex starting materials that is compatible with dense functionality and therefore holds potential, in combination with a click approach, for the easy derivatization of natural products and medicinal compounds is still in demand.

Inspired by our recent study on the oxygenation of 3-oxoesters,[17] and given their inherent reactivity with various electrophiles,[18,19] our goal was to develop a reliable and operationally simple azidation reaction that provides straightforward access to a variety of organic azides. We anticipated

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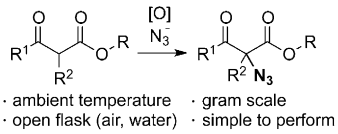
a route to 2-azido-3-oxoesters that would involve selective oxidation of the enolizable position and concomitant introduction of the azide with a suitable azide source as simple as NaN_3 (Scheme 1). The oxidative azidation of 1,3-dicar-

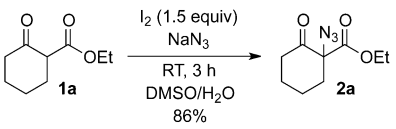


Scheme 1. Envisioned approach to 2-azido-3-oxoesters.

bonyl compounds dates back to the works of Moriarty et al. in 1988, who reported on the hypervalent iodine oxidation of 1,3-diketone compounds in the presence of azidotrimethylsilane;[20] to date, however, this potential has remained largely unrealized with more complex starting materials.[12a,21,22] In this article, we delineate the scope, limitations, and first applications of a novel and highly practical one-step reaction that transforms 1,3-dicarbonyl compounds into their azide-containing analogues with high chemoselectivity.

Results and Discussion

Initial studies and optimization: The 1,3-dicarbonyl motif is ubiquitous in polyketide-derived natural products and is easily synthesized through the application of aldol-type methodologies.[23] To our surprise, a protocol that is simple to perform and that results in the direct azidation of 3-oxoesters and related 1,3-dicarbonyl substrates by the use of simple azide nucleophiles is unknown.[24] Our plan was actualized first when 3-oxoester **1a** was exposed to an excess of sodium azide (approximately 4 equiv) in the presence of iodine (1.5 equiv), being the terminal oxidant, in aqueous DMSO (0.1 M, DMSO/H_2O = 2:1). The reaction reached completion within 3 h at room temperature and furnished the azidated product **2a** in 86% yield after isolation (Scheme 2). This result is interesting because the introduction of the azide smoothly occurs at a tertiary carbon, a task not many methods are successful in.[20–22]



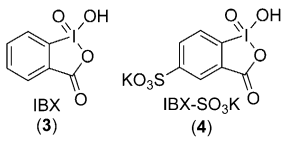
Scheme 2. Initial findings on the formation of 2-azido-3-oxoester **2a**.

In light of this initial discovery, the reaction of 3-oxoester **1a** with NaN_3 to form azido ester **2a** was examined in the presence of a variety of oxidants. It became clear that electrophilic iodine sources in aqueous DMSO performed best (Table 1). Because, occasionally, the use of stoichiometric amounts of I_2 is not truly compatible with highly functionalized molecules,[25] we then investigated the use of catalytic amounts of iodides in the presence of mild oxidants.[26] To this end, 3-oxoester **1a** was treated with various oxidants in an aqueous solution of NaI (0.2 equiv) and NaN_3 (excess) in DMSO. Whereas the use of oxidative agents such as H_2O_2, *tert*-butyl hydroperoxide (TBHP), and oxone was only partially successful (leading either to decomposition or low conversion; Table 1, entries 5–7), 2-iodoxybenzoic acid (IBX; **3**)[27] was found to be an effective oxidant, yielding the desired azide **2a** in excellent yield (91%) after 30 min (Table 1, entry 8). Although IBX is easy to handle and environmentally benign, we felt that the fact that IBX rapidly oxidizes alcohols and many other functionalities might render it less useful for the purpose of chemoselective azidation. In principle, an oxidative agent that parallels the action of IBX on iodide ions would provide a facile and valuable route to 2-azido-3-oxoesters if it is mild enough to tolerate a range of functional groups, including sensitive moieties, such as alcohols, thus obviating the need for protecting-group operations. Consequently, we turned our attention to the newly developed IBX-derivative **4** (IBX-SO_3K), which, at room temperature, is water soluble and fully lacks reactivity towards primary and secondary alcohols (Scheme 3).[28–30] To our delight, 3-oxoester **1a** was rapidly converted into the corresponding azide **2a** when IBX-SO_3K and catalytic amounts of NaI were used to generate the active oxidant in situ (Table 1, entry 9). The procedure for the direct azida-

Table 1. Reaction conditions for the conversion of **1a** into **2a**.

	Conditions	Time [h]	Yield[a] [%]
1	**I_2 (1.5 equiv), NaN_3, RT, DMSO/H_2O**	**3**	**86**
2	I_2 (1.5 equiv), NaN_3, 40 °C, THF/H_2O	24	67
3	I_2 (1.5 equiv), NaN_3, 40 °C, MeCN/H_2O	24	56
4	NIS (1.5 equiv), NaN_3, RT, DMSO/H_2O	3	67
5	H_2O_2, NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O	0.5	decomp.
6	TBHP, NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O	3	no conv.
7	oxone, NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O	3	61
8	IBX (1.5 equiv), NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O	0.5	91
9	**IBX-SO_3K (1.5 equiv), NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O**	**0.5**	**91**
10	IBX-SO_3K (1.5 equiv), NaI (0.2 equiv), NaN_3 (1.1 equiv), RT, DMSO/H_2O	2	90
11	IBX-SO_3K (1.5 equiv), NaBr (0.2 equiv), NaN_3, RT, DMSO/H_2O	4	31
12	IBX-SO_3K (1.5 equiv), NaN_3, RT, DMSO/H_2O	24	<2
13	NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O	24	no conv.
14	IBX-SO_3K (1.5 equiv), Ph_3PBnI (0.2 equiv), NaN_3, RT, EtOAc/H_2O	4	74

[a] Isolated yield after column chromatography.

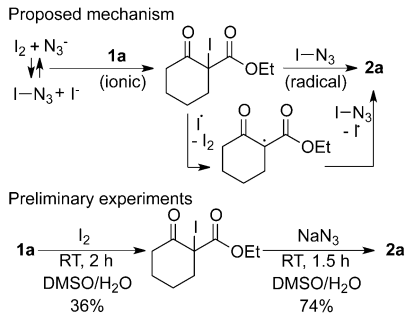


Scheme 3. Structures of IBX and IBX-SO_3K.

tion of 3-oxoesters is very simple: NaI (0.2 equiv) and IBX-SO_3K (**4**; 1.5 equiv) were added to a vigorously stirred solution of **1a** and NaN_3 (excess) in a mixture of DMSO and water at room temperature, followed by workup with an aqueous $Na_2S_2O_3$ solution when the reaction had run to completion. Importantly, through the use of stoichiometric amounts of NaN_3, the yield of the azidation remained high without requiring significantly longer reaction times (Table 1, entry 10). The use of NaBr rather than NaI led to markedly reduced yields (Table 1, entry 11). When Ph_3PBnI was employed as a phase-transfer catalyst, a biphasic mixture of EtOAc and water could be substituted for the DMSO/H_2O solution (Table 1, entry 14).

From this survey, two particularly useful conditions were identified; Method A (IBX-SO_3K (1.5 equiv), NaI (0.2 equiv), NaN_3, room temperature, DMSO/H_2O), and Method B (I_2, NaN_3, room temperature, DMSO/H_2O). Both protocols are simple to perform, are run under air at room temperature, and exhibit broad substrate scope (see below). Due to the mild oxidation power of IBX-SO_3K, Method A is particularly well suited for modifying complex molecules with a multitude of functional groups. Method B, on the other hand, requiring only an inexpensive oxidant (I_2, which has a current price of less than 0.5 Euro per gram) and a very cheap azide source (NaN_3, currently less than 0.3 Euro per gram), proved to be quite scalable with **1a** and delivered 76% yield of the desired product **2a** on a multigram scale (see the Supporting Information).

In the presence of I_2 and NaN_3 (Method B), the net transformation most likely involves two steps, one of which is iodine transfer onto the activated carbon followed by substitution at the tertiary center to give the organic azide. We assume that I_2 or IN_3 are the electrophilic iodine sources responsible for the first step.[14,15] The subsequent substitution might follow a radical mechanism as delineated in Scheme 4;[16,31] however, a classical S_N2 mechanism, as proposed previously even for tertiary carbon atoms adjacent to carbonyl groups, cannot be ruled out.[32,33]



Scheme 4. Proposed mechanism for the reaction with I_2/NaN_3.

Support for the intermediacy of iodinated compounds is gained from the observation that the use of molecular iodine allows for the isolation of ethyl-1-iodo-2-oxocyclohexanecarboxylate when **1a** is reacted with I_2; the substitution with NaN_3 then proceeds quite smoothly to produce **2a** (Scheme 4). Due to the low stability of the 2-iodo-3-oxoester intermediate at room temperature, this two-step sequence provides azide **2a** in poor overall yields, thus demonstrating the experimental advantage of the use of a high-yielding, one-pot protocol (Method B).

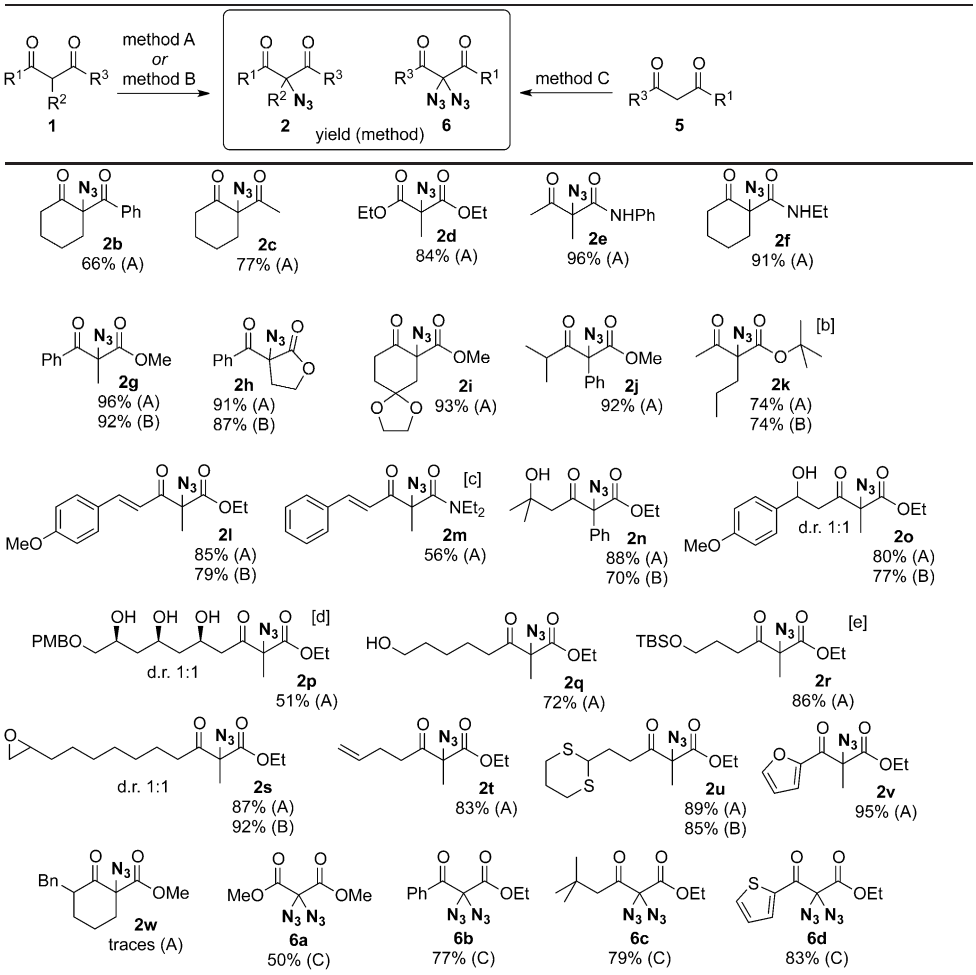
Interestingly, the azidation with IBX-SO_3K/NaI (Method A) showed a dramatically enhanced rate compared to the conversion performed with stoichiometric amounts of I_2.[34] We also note that the results of the NMR experiments do not indicate the intermediary occurrence of ethyl-1-iodo-2-oxocyclohexanecarboxylate when **1a** is reacted according to Method A. Although we feel a detailed discussion of the mechanism in the case of the IBX-SO_3K/NaI system is premature at this point, the introduction of the azide substituent may not be rationalized by a mechanism as discussed above in which IBX-SO_3K would be only responsible for the in situ formation of I_2 through oxidation of iodide. Instead, various hypervalent iodine species appear to be involved, the exact identity of which is under investigation.

Scope and limitations of the direct azidation: Under the two conditions identified in our optimization studies, a range of 1,3-dicarbonyl compounds were reacted with sodium azide. As shown in Table 2, 3-oxoesters, 3-oxoamides (e.g., **2e** and **2f**), malonates (e.g., **2d**), and 3-oxoketones (e.g., **2b** and **2c**), all proved to be viable substrates for the transformation into tertiary azides. In most cases, both Method A and Method B provide the azide products in similar yields. It is worth mentioning that azidation can proceed in the presence of a multitude of functional groups, including acetals, dithianes, silyloxy ethers, epoxides, amides, amines, and olefins, many of which are reactive under traditional azidation conditions.[8–16,20–22] Of primary importance for our purposes, tertiary, secondary, primary, and even benzylic alcohols were tolerated (e.g., **2n**–**p**). At room temperature, reaction times between 30 min and 3 h were typically required to fully convert the starting substrates **1** into the azide-containing products **2**. In some cases, higher temperatures were required; this can be attributed to the low reactivity of the sterically demanding carboxylic acid derivatives (e.g., **2k** and **2m**).[34] To date, almost no other azidation protocol has been shown to have a substrate scope as broad as that shown herein.

Despite the high level of generality, we identified a few limitations with regard to the substrate scope. Primary alkyl halides were subject to azide substitution under the reaction conditions and failed to deliver the desired product. Sterically demanding substituents at the 4-position of 3-oxoesters lead to poor reactivity, even at elevated temperatures (e.g., **2w**).

The reaction was then screened against 1,3-dicarbonyl compounds **5** that do not have an additional substituent at the 2-position (R^2=H). To our surprise, rather stable 2,2-bisazido-1,3-dicarbonyl compounds **6** were easily obtained in good yields after only 10 min reaction under slightly modified conditions (3 equiv of IBX-SO_3K, 0.2 equiv. NaI, NaN_3, RT, DMSO/H_2O; Method C). It is noteworthy that the prod-

Table 2. Scope of the azidation of 1,3-dicarbonyl compounds.[a]



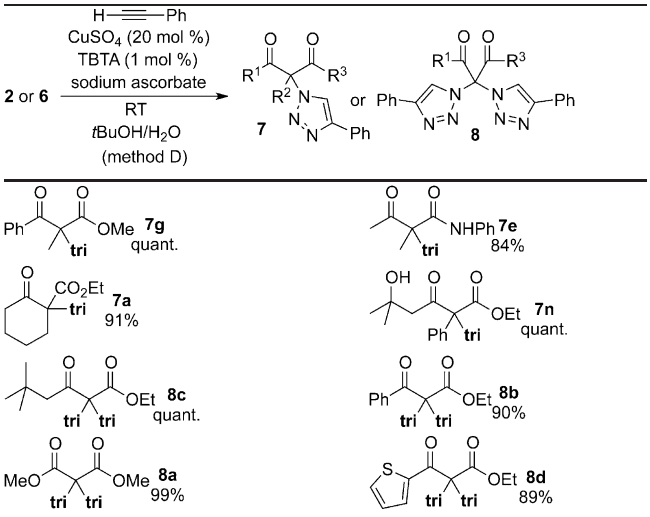
[a] Method A: IBX-SO_3K (1.5 equiv), NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O; Method B: I_2, NaN_3, RT, DMSO/H_2O; Method C: IBX-SO_3K (3 equiv), NaI (0.2 equiv), NaN_3, RT, DMSO/H_2O. See the Supporting Information for reaction times. [b] 40 °C. [c] 50 °C. [d] PMB = 4-methoxybenzyl. [e] TBS = *t*$BuMe_2Si$.

ucts of monoazidation, as reported under the conditions developed by Moriarty and others,[20–22] were not found under these conditions. Extended reaction times resulted in dramatic decomposition of this somewhat neglected class of compounds.[35,36] Although not investigated in detail at this stage, the novel double azidation that took place by using Method C shows promise for tolerating a great variety of functional groups, as does Method A. Interestingly, neither bisazides **6** nor the products of monoazidation were formed from **5** when treated with I_2/NaN_3.

Modifications through a click approach: One strength of this azidation strategy lies in its ability to rapidly deliver azide-containing cores that can be further functionalized by applying standard 1,3-dipolar cycloaddition reactions with terminal alkynes. Because the location of the azido substituents adjacent to two carbonyl groups distinguishes products **2** and **6** from all the other organic azides utilized in click approaches until now,[37] we realized the need to briefly test the viability of the Cu^I-catalyzed azide–alkyne [3+2] cycloaddition[6,7] for their ready modification. To this end, both monoazido and bisazido compounds (**2** and **6**) were treated with phenylacetylene in the presence of $CuSO_4$ (20 mol%), tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA; 1 mol%) and sodium ascorbate (0.4 equiv) in *t*$BuOH/H_2O$ (Method D). As summarized in Table 3, 1,2,3-triazoles **7** were obtained in excellent yields from monoazides **2**. Moreover, bisazides **6** were also converted smoothly into the stable bistriazoles **8**, thus providing easy access to this class of compounds.[38]

It is worth mentioning that introduction of the azide by using Method A can be coupled with triazole formation in a one-pot manner. For example, ester **1a** was directly transformed into 1,2,3-triazole **7a** in 82% yield, thus avoiding the need for isolation of the azido intermediate **2a** or changing the solvent. The one-pot procedure requires an excess of sodium ascorbate to fully reduce the IBX-SO_3K still present from the preceding azidation step: 1) IBX-SO_3K

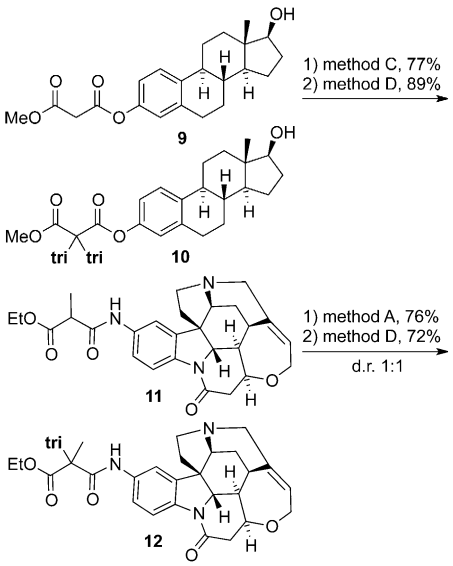
Table 3. Modification of **2** and **6**.[a,b]



[a] Method D: PhC≡CH, $CuSO_4$ (20 mol%), TBTA (1 mol%), sodium ascorbate (0.4 equiv), RT, *t*$BuOH/H_2O$ (1:1). See the Supporting Information for reaction details. [b] **tri** = 4-phenyl-1*H*-1,2,3-triazol-1-yl.

(1.5 equiv), NaI (0.2 equiv), NaN_3 (1.1 equiv), RT, DMSO/H_2O (1:1), 1 h; 2) phenylacetylene (1.1 equiv), $CuSO_4$ (0.2 equiv), TBTA (0.02 equiv), sodium ascorbate (1.6 equiv), RT, 24 h.

Applications to late-stage modifications of complex structures: A striking demonstration of the generality and functional-group tolerance of the title reaction is displayed in the modification of complex target molecules of biological interest. Scheme 5 shows the functionalization of two natural products, β-estradiol (**9**) and strychnine (**11**), attached to 1,3-dicarbonyl units. Although the complex molecules contain sensitive functionalities, such as oxidizable hydroxyl groups, electron-rich alkenes, and nucleophilic nitrogen centers, the formation of the azido derivatives (and the subsequent cycloaddition tested with phenylacetylene) takes place with a high degree of chemoselectivity. In all cases, the modified natural products were formed in good yields under the standard conditions without requiring any protecting groups, thus highlighting the utility of this azidation protocol in the derivatization and late-stage diversification of sensitive structures.



Scheme 5. Applications to natural-product analogues.

Conclusion

A practical method that can be used to achieve the direct azidation of 1,3-dicarbonyl compounds has been developed. By the use of sodium azide as an inexpensive azide source, the starting dicarbonyl compound is oxidized with either I_2 or IBX-SO_3K/NaI. The reaction can be used conveniently from milligram to multigram scales and provides easy access to tertiary 2-azido and 2,2-bisazido-1,3-dicarbonyl compounds, both of which are ideally suited for further functionalization through standard Cu^I-catalyzed [3+2] cycloaddition reactions. Exceptionally high chemoselectivity and functional group tolerance are distinctive features of the azidation reaction and will likely render it a powerful tool for late-stage derivatization of sensitive complex molecules. In combination with a click approach, one can imagine applications in numerous fields of research.

Experimental Section

Method A: Formation of 2a[33b]: Compound **1a** (25.0 mg, 147 μmol) was dissolved in DMSO (1 mL), and aqueous NaN_3 (1 M, 0.5 mL) was added. NaI (4.4 mg, 29.4 μmol, 0.2 equiv) and IBX-SO_3K (87.8 mg, 220 μmol, 1.5 equiv) were added in one portion and the solution was stirred for 30 min at RT. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The reaction mixture was extracted with Et_2O (3×10 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica (pentanes/EtOAc, 95:5). The azido compound **2a** was obtained as a pale-yellow oil (28.1 mg, 133 μmol, 91%). R_f=0.32 (pentanes/Et_2O, 90:10); ^{1}H NMR (250 MHz, $CDCl_3$): δ= 1.32 (t, J=7.1 Hz, 3H), 1.69–1.88 (m, 4H), 1.89–2.03 (m, 1H), 2.37–2.53 (m, 2H), 2.58–2.68 (m, 1H), 4.31 (q, J=7.1 Hz, 1H), 4.31 ppm (q, J= 7.1 Hz, 1H); ^{13}C NMR (91 MHz, $CDCl_3$): δ=14.3, 21.5, 26.6, 35.6, 39.8, 62.9, 74.1, 167.8, 202.6 ppm; IR (film): $\tilde{\nu}$=2943, 2870, 2108, 1728, 1448, 1234, 1142, 1094, 1012, 855 cm^{-1}; MS (EI): m/z (%): 183 (1) [M^+-N_2], 110 (68), 82 (100), 55 (70). HRMS (EI): m/z calcd for $C_9H_{13}O_3N$ [M^+-N_2]: 183.0890; found: 183.0887.

Method B: Formation of 2a[33b]: Compound **1a** (25.5 mg, 150 μmol) was dissolved in DMSO (1 mL), and aqueous NaN_3 (1 M, 0.5 mL) was added. I_2 (57.1 mg, 225 μmol, 1.5 equiv) was added and the solution was stirred for 4 h at RT. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The reaction mixture was extracted with Et_2O (3×10 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica (pentanes/EtOAc, 95:5). The azido compound **2a** was obtained as a pale-yellow oil (27.4 mg, 130 μmol, 86%).

Method C: Formation of 6a:[20,35] Dimethyl malonate (20.0 mg, 151 μmol) was dissolved in DMSO (1 mL), and aqueous NaN_3 (1 M, 0.5 mL) was added. NaI (4.5 mg, 30.0 μmol, 0.2 equiv) and IBX-SO_3K (176.6 mg, 454 μmol, 3.0 equiv) were added and the solution was stirred for 10 min at RT. The reaction was quenched by the addition of a saturated aqueous $Na_2S_2O_3$ (10 mL). The reaction mixture was extracted with Et_2O (3× 10 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica (pentanes/EtOAc, 90:10). The bisazido compound **6a** was obtained as a pale-yellow oil (16.0 mg, 74 μmol, 50%). R_f=0.40 (pentanes/EtOAc, 80:20); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.92 ppm (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): δ=54.6, 80.1, 164.1 ppm; IR (film): $\tilde{\nu}$=2963, 2920, 2850, 2360, 2123, 1759, 1437, 1297, 1237, 1070, 1049, 790, 732 cm^{-1}. Direct mass analysis of the bisazido compound was not possible. The MS and HRMS data of bistriazole **8a** derived from **6a** are given below.

Method D: Formation of 8a: Bisazido compound **6a**[35] (15.7 mg, 73.3 μmol) was dissolved in a 2:1 mixture of *t*BuOH and water (250 μL). Phenylacetylene (17.7 μL, 16.5 mg, 161 μmol, 2.2 equiv), $CuSO_4$·$5H_2O$ (3.7 mg, 14.7 μmol, 0.2 equiv), sodium ascorbate (5.8 mg, 29.3 μmol, 0.4 equiv), and TBTA (0.8 mg, 1.5 μmol, 2 mol%) were added, and the solution was stirred at RT for 1 h. The reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by flash chromatography on silica (pentanes/EtOAc, 80:20) to give **8a** as a white solid (30.4 mg, 72.7 μmol, 99%). R_f= 0.27 (pentanes/EtOAc, 80:20); ^{1}H NMR (360 MHz, $CDCl_3$): δ=4.09 (s,

6H), 7.31–7.36 (m, 2H), 7.38–7.43 (m, 4H), 7.80–7.85 (m, 4H), 8.46 ppm (s, 2H); ^{13}C NMR (91 MHz, $CDCl_3$): $\delta = 55.4$, 79.7, 120.6, 126.0, 128.9, 129.0, 129.5, 148.4, 161.2 ppm; MS (ESI): *m/z* (%): 361 (100), 282 (70); HRMS (ESI): *m/z* calcd for $C_{19}H_{17}O_2N_6^{2+}$ $[M-CO_2Me+2H^+]$: 361.1402; found: 361.1402.

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