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Azidation of β-carbonyl lactones and lactams

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ABSTRACT

The direct azidation of various heterocyclic β-ketoesters, lactones, and lactams is reported. By using tosylazide and an organic base such as L-proline or TBD, the direct α-insertion of azide into these substrates was achieved in moderate to good yields, without competitive deacylating diazo transfer. This procedure represents an interesting alternative to the usual two-step approach of α-halogenation and subsequent displacement with azide ion.

The high versatility of organic azides made them very useful in organic synthesis. They are reported to react with electrophiles, nucleophiles, and radical species and to yield reactive nitrenes under thermal and photochemical conditions.[1] Azides are easily converted into amines by the Staudinger reaction,[2] and are useful for the preparation of various types of heterocycles.[3] Furthermore, they act as 1,3-dipoles in cycloaddition reactions and have been extensively used in the highly robust Huisgen azide–alkyne 1,3-dipolar cycloaddition under thermal activation or under Cu(I) catalysis.[4]

In the course of our synthetic work we envisioned direct azidation of heterocyclic β-ketoesters (Scheme 1, X = O) by using sulfonyl azides. Heterocyclic β-ketoesters have been extensively studied in synthetic chemistry,[5] that is, in various C-alkylation reactions,[5a] electrophilic amination,[5b,c] halogenations,[5d] or for addition to Michael acceptors.[5e–g] Surprisingly, studies devoted to their direct azidation have not been reported in the literature thus far (Scheme 1, path b). The closest related works have mentioned the reactivity of sulfonyl azides with carbocyclic β-ketoesters (Scheme 1, X = CH_2).[6] These studies revealed two-competitive reactions: the usually major deacylating diazo transfer (Scheme 1, pathway a) and the minor azido group transfer reaction (Scheme 1, pathway b).[6] The ratio between these two possible pathways depends on the nature of the sulfonyl azide reagent and on the nature of the substrate; the azido group transfer reaction being the dominant transformation only when extended cyclic or hindered substrates are engaged (Fig. 1).[6a,c]

Given our synthetic constraints, we sought a direct azidation reaction, instead of a two-step procedure through α-halogenation and subsequent displacement of halide with azide ion.[7] Considering the above-mentioned literature data, we anticipated that the study of the reactivity of sulfonyl azides toward a collection of heterocyclic β-ketoesters (Scheme 1, X = O, NH) would be of interest to the synthetic community.

In preliminary experiments, our model substrate 2-acetyl-γ-butyrolactone **1a** was treated under two reported conditions: by

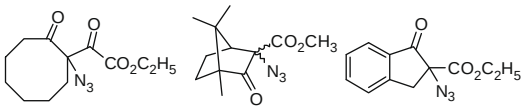
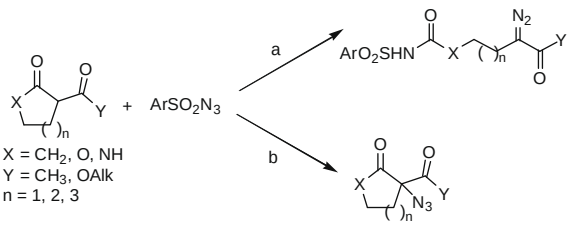


Figure 1. Examples of reported azidocarbocyclic β-ketoesters.



Scheme 1. Reactivity of sulfonyl azides toward heterocyclic and carbocyclic β-ketoesters.

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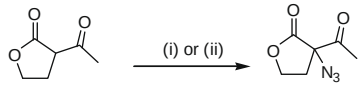
generating triflic azide in situ,[8] and by using a combination of trimethylsilylazide and iodosobenzene.[9] Both these conditions gave the desired azido transfer product **2a** in poor yield (32% and 5%, respectively, Scheme 2).

We then focused on the use of commercially available tosylazide (TsN_3) with organic bases. First, we followed the conditions used for the preparation of examples shown in Figure 1. However, in the presence of 1 equiv of TsN_3 and 1 equiv of TEA (triethylamine) or DBU (1,8-diaza-bicyclo[5,4,0]undec-7-ene) no reaction was observed after 72 h in DCM (Table 1, entries 1 and 2). Changing the base to TBD (1,5,7-triazabicyclo[4.4.0]dec-1-ene), previously studied by our group for its high reactivity,[10] afforded the expected azido product **2a** in moderate to good yields in DCM, toluene, and THF (Table 1, entries 3–5). We then turned our attention to L-proline, known to be a good activator of 1,3-dicarbonyl compounds.[11] Treating **1a** with 1 equiv of TsN_3 and 1 equiv of L-proline in DMF for 72 h at room temperature afforded **2a** in 52% of yield (Table 1, entry 6). The best azidation result was obtained by changing the solvent to DMSO, affording in this case, the desired azidation product **2a** in 62% yield along with the recovery of 15% of the starting material (Table 1, entry 7). The use of both reagents in excess did not change the efficiency of the reaction. Importantly, in none of these reactions were the products of the competitive deacylating diazo transfer reaction detected (Scheme 1).

Having successfully synthesized the azido derivative of 2-acetyl-γ-butyrolactone **1a**, we moved our attention toward demonstrating the generality of the strategy starting from various heterocyclic β-ketoesters, lactones, and lactams. Compounds **1b–d** were prepared following the literature procedures,[12] whereas compound **1e** is commercially available. When treated under the optimized conditions in the presence of L-proline, five-membered lactone **1b** and five-membered lactam **1c** afforded the desired azido compounds **2b** and **2c** in moderate yields (Table 2, entries 1 and 2). Lower yields (<20%) were obtained using TBD, DBU, or TEA as base (in DCM) instead of L-proline. For six-membered lactams **1d–e**, L-proline failed to afford the desired azidation products in acceptable yields. In both cases, the starting material conversion was very low, only **2d** could be obtained in 12% yield (Table 2, entries 3 and 6). Surprisingly, in the case of **1d–e**, the use of TBD or DBU improved the formation of the azidation products **2d–e** to a large extent (Table 2, entries 4–5 and 7–8). All the resulting azides were characterized from spectral data.[13] It is noteworthy to mention that in none of these reactions the deacylating diazo transfer adduct (Scheme 1, pathway a) was formed in an isolable amount. Instead, the unreacted starting material could be recovered almost quantitatively.

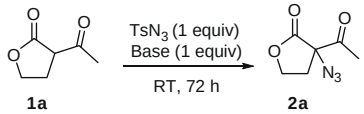
Considering the above-mentioned results, it appears that the azidation reaction is highly sensitive to the substrate's structure and this preliminary study did not allow us to draw any general conclusions. Yields were found to be reproducible, but depending on the base used, the outcome of the reaction is not easily predictable.

Finally, compound **2e** was used in further transformations to assay the azide moiety reactivity. Under classical Staudinger reaction conditions the azido compound **2e** could be converted into the amino product **3**, in a moderate but non-optimized yield (Scheme 3).[14] Moreover, as an example of click reaction, **2e** was engaged in a Huisgen azide–alkyne 1,3-dipolar cycloaddition catalyzed by Cu(I),



Scheme 2. Azidation of 2-acetyl-γ-butyrolactone **1a** using literature methods.

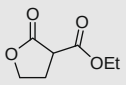
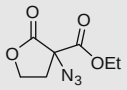
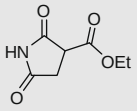
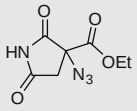
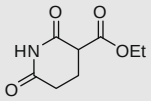
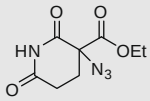
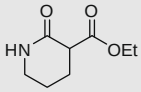
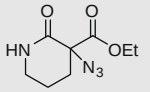
Table 1
Azidation of 2-acetyl-γ-butyrolactone **1a**



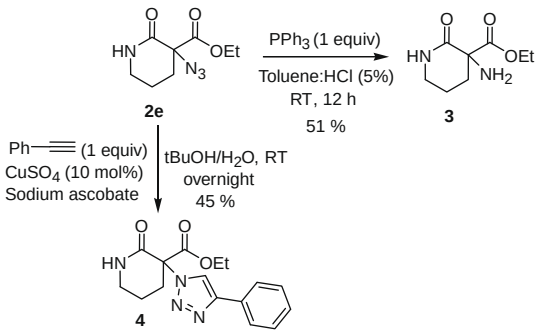
Entry	Base	Solvent	Yield[a] (%)
1	TEA	DCM	0
2	DBU	DCM	0
3	TBD	DCM	42
4	TBD	Toluene	38
5	TBD	THF	56
6	L-Pro	DMF	52[b]
7	L-Pro	DMSO	62[b]

[a] Yields are reported for pure products.
[b] Racemic compound.

Table 2
Azidation of selected heterocyclic β-ketoesters[a]

Entry	Substrate		Base	Solvent	Product		Yield[b] (%)
1		**1b**	L-Pro	DMSO		**2b**	38
2		**1c**	L-Pro	DMSO		**2c**	30
3		**1d**	L-Pro	DMSO		**2d**	12
4			TBD	DCM			66
5			DBU	DCM			52
6		**1e**	L-Pro	DMSO		**2e**	0
7			TBD	DCM			78[c]
8			DBU	DCM			83[c]

[a] TsN_3 (1 equiv), base (1 equiv), 72 h at rt.
[b] Yields are reported for pure products.
[c] 48 h at rt.



Scheme 3. Reactivity of azido compound **2e**.

with phenylacetylene affording compound **4**, in a medium but non-optimized yield (Scheme 3).[15]

In conclusion, direct azidation of heterocyclic β-ketoesters using TsN_3 and organic bases was studied. Each selected substrate could be converted into the azido derivative in moderate to good yields. It appears that base plays a critical role in the outcome of the reaction. Results showed that L-proline should be preferred for the azidation of five-membered rings and TBD or DBU are more appropriate for the conversion of six-membered rings. Thus, it appears that direct azidation of heterocyclic β-ketoesters is a potent alternative to the standard two-step procedure (halogenation and displacement with azide ion).

Acknowledgments

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12. Hamashima, Y.; Ishikura, K.; Kubota, T.; Minami, K. US Patent 4,578,378, 1986.
13. *General procedure for the azidation reaction:* To a solution of γ-butyrolactone **1a** (100 mg, 0.7 mmol) in dry DMSO (5 mL) was added TsN_3 (153 mg, 0.7 mmol) followed by L-proline (89 mg, 0.7 mmol) and the mixture was allowed to stir at rt for 72 h. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography. Elution of the column with ethylacetate:cyclohexane (2:8) gave the desired azidation product **2a** as a colorless liquid (81 mg, 62%). *Spectral data for azidation product* **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27–2.36 (m, 1H), 2.43 (s, 3H), 2.71–2.79 (m, 1H), 4.33–4.47 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 32.4, 66.4, 72.8, 170.7, 200.4.; IR (Neat): 2107, 1765, 1722, 1359, 1219, 1191, 1166, 1019 cm^{-1}.; LC–MS (CI): 170.1 (M+1); **2b**: (^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, *J* = 4.56 Hz, 3H), 2.28 (quintet, *J* = 4.58 Hz, 1H), 2.76 (quintet, *J* = 3.74 Hz, 1H), 4.34 (q, *J* = 4.8 Hz, 2H), 4.39–4.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.4, 33.7, 64.0, 66.9, 167.1, 171.1; IR (Neat): 2117, 1776, 1746, 1242, 1214, 1172, 1117, 1020, 909, 729 cm^{-1}; LC–MS (CI): 200.1 (M+1); **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, *J* = 5.2 Hz, 3H), 2.68 (d, *J* = 18.4 Hz, 1H), 3.1 (d, *J* = 18.0 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 8.69 (br s, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 41.0, 64.5, 67.4, 166.6, 172.0, 173.1; IR (Neat): 3268, 2986, 2120, 1715, 1368, 1267, 1234, 1182, 1051, 732, 696 cm^{-1}; LC–MS (CI): 213 (M+1); **2d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, *J* = 3 Hz, 3H), 2.01–2.08 (m, 1H), 2.40–2.48 (m, 1H), 2.64–2.76 (m, 2H), 4.32–4.39 (q, *J* = 3 Hz, 2H), 8.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 27.5, 28.2, 64.0, 67.3, 167.2, 167.3, 171.1; IR (Neat): 3242, 3106, 2985, 2117, 1702, 1354, 1232, 1187, 1095, 1048, 729 cm^{-1}; LC–MS (CI): 227 (M+1); **2e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, *J* = 6 Hz, 3H), 1.87–2.00 (m, 3H), 2.16–2.29 (m 1H), 3.37–3.45 (m, 2H), 4.27–4.43 (m, 2H), 7.02 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 17.9, 30.6, 41.7, 62.3, 67.5, 166.2, 168.7; IR (Neat): 3249, 2941, 2869, 2120, 1744, 1670, 1486, 1239, 1196, 1107, 1052, 1014 cm^{-1}; LC–MS (CI): 213 (M+1).
14. *Procedure for the reduction of azide* **2e***:* To a solution of **2e** (50 mg, 0.23 mmol) in toluene (0.5 mL) was added triphenylphosphine (0.19 mmol, 50 mg). The reaction was stirred for 5 min at rt then a solution of HCl 5% (0.5 mL) was added. The solution was stirred overnight then extracted with DCM (2 × 2 mL), the aqueous layer was basified with NaOH (1 N) and extracted with DCM (3 × 3 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give compound **3** (22 mg, 51%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 6 Hz, 3H), 1.82–2.02 (m, 5H), 2.20–2.25 (m 1H), 3.38–3.42 (m, 2H), 4.20–4.29 (m, 2H), 6.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.1, 33.4, 42.6, 61.9, 62.0, 170.6, 174.0; IR (Neat): 3227, 2942, 1731, 1666, 1195, 730 cm^{-1}; LC–MS (APCI): 187 (M+1).
15. *Procedure for the click reaction with* **2e***:* To a solution of azide **2e** (54 mg, 0.17 mmol) in a mixture tBuOH/H_2O 4/1 (8 mL) were added phenylacetylene (26 mg, 0.17 mmol), sodium ascorbate (10 mg, 0.034 mmol), and $CuSO_4$ (6 mg, 0.017 mmol). The mixture was stirred overnight at rt then extracted with EtOAc (2 × 10 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography. Elution of the column with ethylacetate:cyclohexane (3:7) gave the desired triazole **4** as a colorless liquid (24 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 6 Hz, 3H), 1.94–1.97 (m, 2H), 2.62–2.69 (m 1H), 3.45–3.47 (m, 3H), 4.19–4.26 (m, 2H), 6.21 (br s, 1H), 7.23–7.27 (m, 1H), 7.33–7.37 (m, 2H), 7.78–7.81 (m, 2H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.4, 29.5, 42.6, 63.2, 70.4, 121.9, 125.8, 128.1, 128.8, 130.6, 147.4, 164.8, 167.9; IR (Neat): 3249, 2930, 2122, 1747, 1678, 1254, 1200, 732, 694 cm^{-1}; LC–MS (APCI): 315 (M+1).