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Michael addition reactions of α-acyloxy nitrile anions

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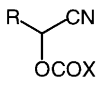
Abstract

The Michael addition reactions of α-acyloxy nitrile anions with Michael acceptors are followed by a shift of the acyl group to the α-carbon of the Michael acceptor. Michael acceptors such as acrylates, acrylonitrile and methyl vinyl ketone can be used. Acetoxy nitriles are selectively deprotonated α to the nitrile.

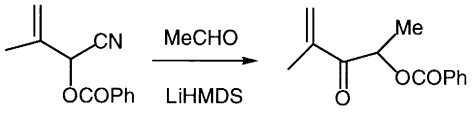
In comparison with other acyl carbanion equivalents such as dithianes and nitro groups, nitrile carbanions substituted by heteroatom functional groups in the α-position have seen little use in organic synthesis. Cyanohydrin ethers have been employed in intermolecular reactions as acyl carbanion equivalents.[1,2] Recently we demonstrated an intramolecular cyclization of the anion of a silylated cyanohydrin with a ketone.[3] Related work has led to the use of cyanophthalides for the regiospecific synthesis of polycyclic quinones.[4]

Hoffman and coworkers prepared α-acyloxy nitriles in one step by the reaction of acyl cyanides with aldehydes.[5] Using Hoffman's conditions, we synthesized α-acyloxy nitriles **1**, **2**, **3** and **4** in 62%, 65% 36% and 52% isolated yields, respectively.



1: R = methyl, X = Ph
2: R = isopropenyl, X = Ph
3: R = 1-propenyl, X = Ph
4: R = isopropenyl, X = Me

Carbanions of α-acyloxy nitriles such as **1** have not been reported. Deprotonation of these nitriles with a strong base such as LDA or lithium hexamethyldisilazane (LiHMDS) would likely be rapid. Nitrile **2** and acetaldehyde were reacted with LiHMDS at −78°C (Scheme 1).



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Scheme 1.

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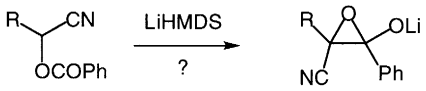
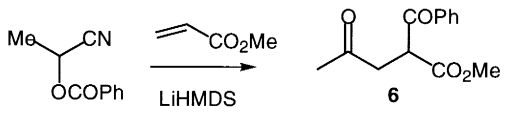
The product, **5**, was produced in 67% yield. The choice of base proved to be crucial, since the reaction with lithium diisopropylamide afforded unidentifiable product mixtures. Unexpectedly, the order of the addition of the reagents was also important, because attempts to prepare the α-benzoyloxy nitrile anion in the absence of the aldehyde led to degradation of the compound, possibly via the intermediacy of the alkoxy epoxide intermediate shown in Scheme 2.[6]



Scheme 2.

However, when a mixture of the aldehyde and the nitrile was treated with LiHMDS, product **5** was isolated as essentially the only product. Ketone **5** is produced from the initial alkoxide product by an intramolecular acyl shift of the benzoyl group followed by the elimination of cyanide ion. The alkoxide of a cyanohydrin is well known to be unstable and rapidly generates the ketone.

If the anion of nitrile **1** were effective as a donor in the Michael addition reaction, the anion produced as a result of the Michael addition might also undergo addition to the benzoyloxy group, providing the adduct **6**. Nitrile **1** reacted with methyl acrylate and LiHMDS at −78°C to produce adduct **6** (Scheme 3) in 65% isolated yield, the result of a Michael addition followed by an intramolecular shift of the benzoyl group and the generation of a ketone.[7]



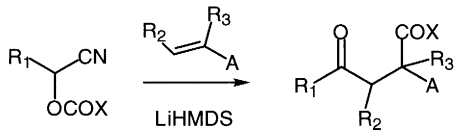
Scheme 3.

This addition reaction is applicable to several base-sensitive Michael acceptors, including methyl vinyl ketone. The reactions of nitriles **1**, **2**, **3** and **4** with Michael acceptors are depicted in Table 1.[8] Interestingly, the α-acyloxy nitrile carbanions react in good to excellent yield with substituted acrylates, acrylonitrile and unsaturated ketones. The Michael addition reactions are always accompanied by the shift of the acyl group followed by the generation of the ketone.

The results shown in Table 1 indicate that α-acyloxy nitrile carbanions can be successfully employed in Michael addition reactions. The Michael acceptors with a β-substituent reacted better than Michael acceptors with an α-substituent. This is counter to the usual observations in Michael addition reactions. Perhaps the Michael acceptors without an α-substituent afforded better yields because the acyl transfer step proceeded more effectively. In those cases where the Michael acceptor does not have an α-substituent, the acyl transfer step produces a β-keto nitrile that can form a stable anion. Remarkably, in the final three entries in Table 1, deprotonation α to the nitrile occurred selectively in the presence of the acetoxy group.

The results of the addition reactions described above demonstrate some synthetic utility of α-acyloxy nitrile carbanions. The ease of preparation of α-acyloxy nitriles, their selective deprotonation and their reactions under mild reaction conditions combine to make them convenient synthetic building blocks. The products of the novel tandem Michael addition–acyl transfer–decyanation reaction[9] are generated in good yields.

Table 1
Reaction of **4a**–**c** with Michael acceptors



X	R_1	R_2	R_3	A	% Yield
Ph	Me	H	H	CO_2Me	65
Ph	Me	H	Me	CO_2Me	51
Ph	Me	H	H	CN	62
Ph	Me	H	Me	CN	21
Ph	Me	Me	H	CO_2Et	58
Ph	CH_2=C(Me)	H	H	CO_2Me	88
Ph	CH_2=C(Me)	H	Me	CO_2Me	41
Ph	CH_2=C(Me)	H	H	CN	55
Ph	CH_2=C(Me)	H	Me	CN	26
Ph	CH_2=C(Me)	Me	H	CO_2Et	57
Ph	CH_2=C(Me)	H	H	COMe	25[a]
Ph	CH_2=C(Me)	H	H	COMe	87[b]
Ph	CH_3CH=CH	H	H	CO_2Me	85
Ph	CH_3CH=CH	H	Me	CO_2Me	48
Ph	CH_3CH=CH	H	H	CN	55
Ph	CH_3CH=CH	H	Me	CN	32
Ph	CH_3CH=CH	Me	H	CO_2Et	64
Me	CH_2=C(Me)	H	H	CO_2Me	82
Me	CH_2=C(Me)	H	Me	CO_2Me	78

a without HMPA - major product resulted from 1,2-addition
b with HMPA.

Acknowledgements

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6. This rearrangement is analogous to the Favorski rearrangement.
7. Representative procedure: To a solution of cyanohydrin ester (1 equiv.) and Michael acceptor (1.2–1.6 equiv.) in THF at −78°C was added dropwise LiHMDS (1.2 equiv.) over 10 min. The reaction was stirred at −78°C for 2 h and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo to provide a residue which was purified by column chromatography using hexanes:ethyl acetate. Adduct of **2** with methyl acrylate: ^{1}H NMR ($CDCl_3$) 1.78–1.79 (m,

3H), 3.34–3.52 (m, 2H), 3.60 (s, 3H), 4.91–4.96 (dd, J=6, 15 Hz, 1H), 5.77–5.78 (m, 1H), 6.03 (s, 1H), 7.39–7.44 (m, 2H), 7.49–7.54 (m, 1H), 7.98–8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) 17.5, 37.4, 48.5, 52.7, 125.9, 128.8, 128.9, 133.7, 136.0, 143.7, 169.8, 194.8, 198.4. HRMS m/z for $C_{15}H_{16}O_4$ calcd 260.1049, found 260.1047. Adduct of **4** with methyl acrylate: ^{1}H NMR ($CDCl_3$) 1.84–1.85 (m, 3H), 2.39 (s, 3H), 3.19–3.27 (dd, 1H, J=18, 5.6 Hz), 3.40–3.49 (dd, 1H, J=18, 8.3 Hz), 3.74 (s, 3H), 4.0–4.1 (dd, 1H, J=5.6, 8.3 Hz), 5.82 (m, 1H), 6.06 (s, 1H). ^{13}C NMR: 17.4, 30.2, 36.5, 52.7, 53.6, 125.8, 143.6, 169.4, 198.6, 202.4. HRMS m/z for $C_{10}H_{14}O_4$ calcd 198.2120, found 198.2115.

8. All compounds exhibited spectra (^{1}H NMR, ^{13}C NMR and high resolution mass spectra/elemental analysis) in accord with the assigned structures.
9. For a review of tandem reactions, see Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159.