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Chemoselective Reduction of α-Cyano Carbonyl Compounds: Application to the Preparation of Heterocycles

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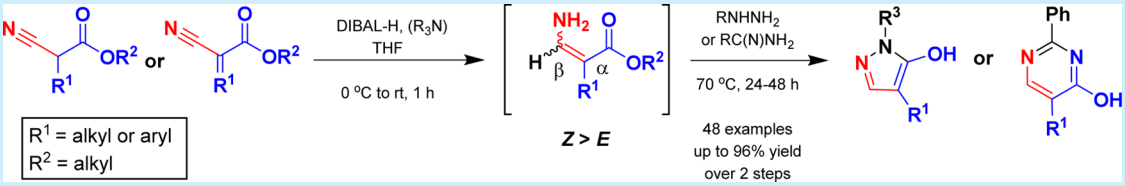
Supporting Information



ABSTRACT: β-Aminoacrylates are reactive intermediates that are useful building blocks in synthesis. General methods for their preparation typically afford α and β disubstitution patterns or β only. Molecules with only α-substituents (β-hydrogen) are much less well-known. A chemoselective reductive tautomerization of α-cyanoacetates, using DIBAL-H, has been developed to access these valuable synthons. α,β-Unsaturated cyanoacetates and α-cyanoketones can, also, be selectively reduced via this methodology. A series of heterocycles were prepared using these β-enamino carbonyl compounds.

β-Aminoacrylates (**1**, Figure 1), a class of masked β-dicarbonyl compounds, are reactive intermediates that are useful synthetic building blocks. The conjugation of enamine and ester gives functionality that can participate in bond-forming reactions via a number of different pathways. These substrates have found their greatest utility in the construction of heterocycles for which there are three general routes. Nucleophiles, such as hydrazines, may add in a conjugate manner to the double bond (with loss of the original β-amine) followed by attack of the distal hydrazine nitrogen at the carbonyl to generate pyrazoles (**2a**; Z, X = N).[1] The β-amine can be derivatized (e.g., by acylation) and then cyclize onto the ester to form heterocycles such as pyrimidines (**2b**; Y = CO; X, Z = N).[2] Finally, the enamine may react to form heterocycles (**2c**) without ester participation.[3] In addition, these substrates are also useful, directly or via *N*-acyl derivatives, in the synthesis of β-amino acids (**3**).[4] Those reactions, among others, show that β-enaminoesters are valuable synthons, and consequently, new methods for their generation are important synthetic tools.

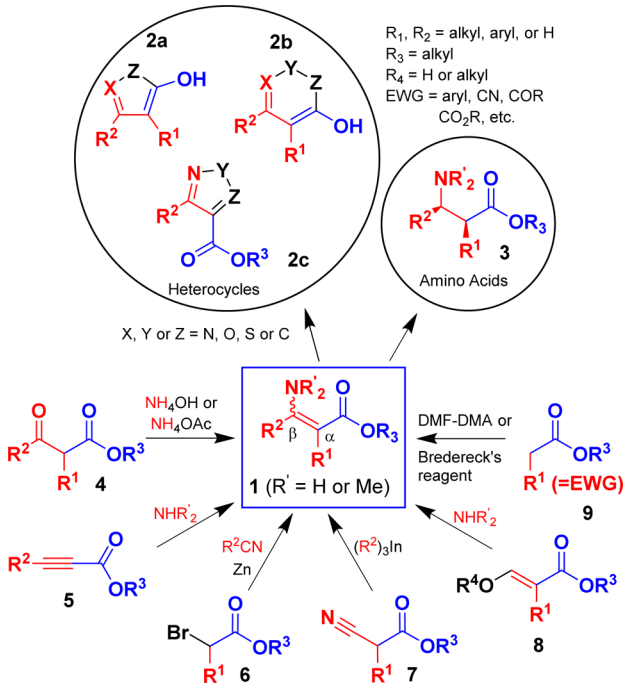


Figure 1. β-Aminoacrylates: preparation and uses.

Numerous methods have been reported for the synthesis of β-aminoacrylates (see Figure 1). Most of these generate acrylates with a β-carbon substitution (**1**, $R_2 \neq H$; **4**,[5] **5**,[6] **6**,[7] **7**[8]). Far fewer reactions produce substrates with a β-hydrogen. Those that are known are limited in scope and either proceed through reactive intermediates, which are typically formed in moderate yields from esters (**8**),[9] or work only with substrates containing an active α-methylene group (**9**).[10] A more general methodology to make β-unsubstituted (**1**; $R_2 = H$) analogues would therefore be of use. Herein, we describe the development of such a reaction.

While engaged in efforts supporting a drug discovery program, we made an unexpected observation. We had an interest in developing a selective partial reduction of a common program intermediate (**10**, Scheme 1). In our attempts to make either the α-formyl ester or α-formylnitrile, we subjected the cyanoester to a variety of reducing agents and conditions (e.g., $LiALH_4$, $NaBH_4$, $LiBH_4$, Red-AL, H_2, etc.) In all but one case, we either observed selective reduction of the ester (to alcohol)

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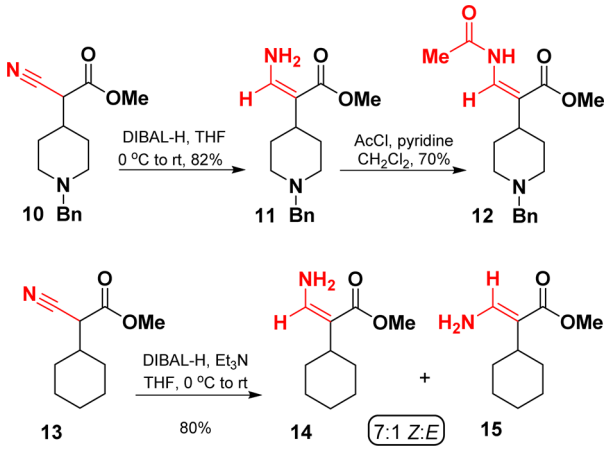
Scheme 1. Chemoselective Nitrile Reduction



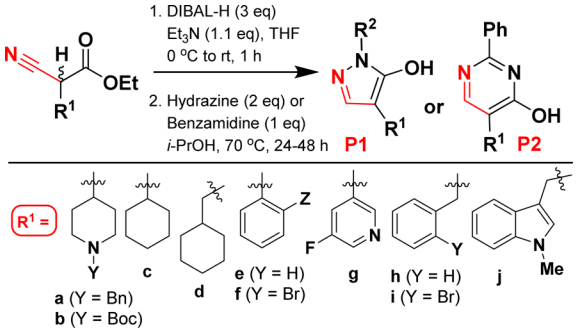
or nitrile (to amine)[11] or a complex mixture due to partial or over-reduction of both groups. However, treatment of cyanoester **10** with DIBAL-H (3 equiv) in THF at 0 °C followed by warming to ambient temperature gave a single product. ^{1}H NMR (in $CDCl_3$) showed the ester remained, the α-proton disappeared, and a new downfield proton formed (δ 6.66, triplet; 10.75 Hz). In addition, the mass of the isolated product was 1 amu lower than the formyl ester. The data were consistent with the formation of β-aminoacrylate **11**. Acylation of the product gave amide **12**, wherein the alkene proton was a doublet (δ 7.39, 11.1 Hz) and confirmed the unusual result. The olefin geometry of both compounds was found (via ^{1}H NMR NOE) to be exclusively *Z*. While the reduction did not result in either of the intended targets, this chemoselective reductive-tautomerization was nonetheless interesting and worth further investigation.

The reduction of an α-cyanoacetate to β-aminoacrylate, such as **11**, is not totally without precedent and has been described for a series of purine-derived α,β-unsaturated α-cyanoacetates under hydrogenolytic conditions.[12] The isolation of β-aminoacrylates was likely substrate dependent as α-cyanoacetates are normally converted to β-aminoesters under those conditions.

In exploring the generality of the reaction, we subjected a simplified substrate (**13**) to the same conditions as cyanoester **10**. The reaction did not produce the expected enamine. Instead, a complex mixture, due to over-reduction of both the nitrile and ester, resulted. The key difference between cyanoesters **10** and **13** is the lack of a basic *tertiary* amine. Repeating the reaction in the presence of triethylamine (1.1 equiv) produced the expected enamine cleanly, as a mixture of isomers (**14** and **15**), in a 7:1 ratio favoring the *Z* isomer.[13] The reaction can be effected with other tertiary amines (e.g., *N*-methylmorpholine, N-ethylpiperidine, etc.), but triethylamine was used throughout due to its higher volatility and, hence, ease of removal.

To examine the scope of the reaction, a series of α-cyanoacetates were reduced by addition of DIBAL-H to a solution of substrate in THF at 0 °C in the presence of triethylamine (see Table 1). An excess (2.5−3.0 equiv) of DIBAL-H was typically employed to ensure the reaction was driven to completion. After addition, cooling was removed and the reaction was stirred at ambient temperature for 30−60 min before the reaction was quenched by the method of Fieser.[14] Enamine formation is generally quantitative. Lower yields may result if aluminum salts formed during the reaction are not fully

Table 1. Scope of Heterocycles from Cyanoesters[a,b]



reactant	R^1 group	product(s)		isolated yield (%)	
		P1	P2	P1	P2
16	**a**	**26**	**27**	80	64
17	**b**	**28**		40	
18	**c**	**29**	**30**	64	77
19	**d**	**31**	**32**	78	73
20	**e**	**33**	**34**	87	63
20	**e**	**35**[b]		95	
21[a]	**f**	**36**		87	
22	**g**	**37**		65	
23	**h**	**38**	**39**	71	90
24	**i**	**40**	**41**	75	80
25	**j**	**42**	**43**	74	68

[a]Methyl ester. [b]P1 N-substitution: R^2 = H, except for **35**, where R^2 = Ph.

hydrolyzed. The aminoacrylates are reasonably stable on cold storage but are prone to tautomerization under acidic conditions, including silica gel, or on standing at rt for extended periods (>1−2 weeks). In all cases, the olefin geometry favored the *Z* isomer, but the ratio is dependent on structure and reaction workup conditions. *Z*:*E* selectivity typically ranges from 5:1 to >60:1. ^{1}H NMR readily distinguishes the isomers.[15] Most intermediates are oils for which complete solvent removal is difficult. Consequently, they are used directly in subsequent steps without further purification.

A series of pyrazoles and pyrimidines were smoothly generated by heating the acrylate intermediates with hydrazine or benzamidine in alcohol solvents for 24 or 48 h, respectively. Most of the products could be cleanly isolated via precipitation on addition of the reaction to water or aqueous pH 7 buffer. The yields over the two steps were generally good to excellent. The poor yield of compound **28** appears to be the result of reaction of the Boc group with hydrazine as condensation with benzamidine provides much better conversion (see compound **65**).

In a manner similar to that for the chemoselective reduction of α-cyanoacetates, it was found that α-cyanoketones can be reduced to β-aminoenones and converted to heterocycles under the same conditions (see Scheme 2). Unlike the previous case, where no ester reduction was seen, ketone reduction can be competitive. The best substrates tend to be acetophenone derivatives. In order to understand the cause of the loss of chemoselectivity in the reduction reaction, we undertook an examination of the reaction mechanism.

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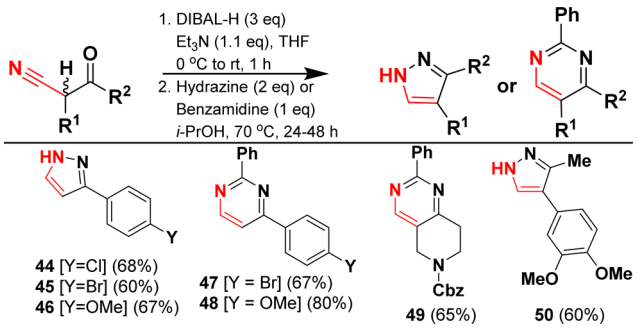
Scheme 2. Cyanoketone Reduction/Heterocycle Formation



ReactIR[16] (Figure 2) was used to explore the reduction mechanism. During the addition of DIBAL-H a gas is evolved.

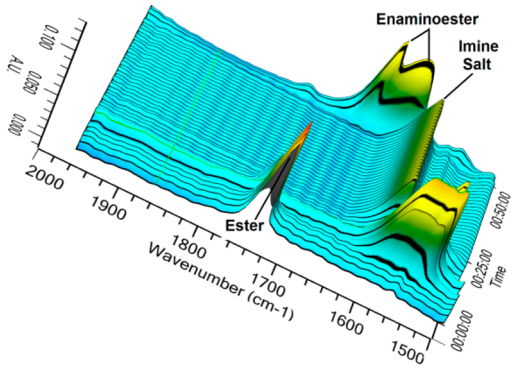
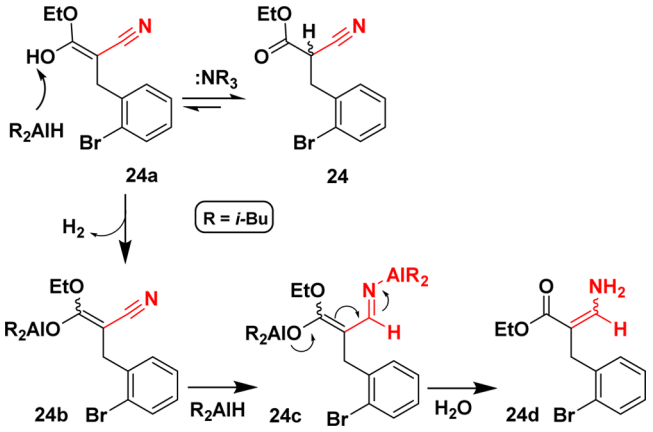


Figure 2. ReactIR of saturated cyanoester reduction (**24**).

We suspect the base, which is necessary for chemoselectivity, promotes formation of the ester tautomer (**24a**), which then reacts with DIBAL-H to give metal enolate **24b** and liberate hydrogen (Scheme 3). The protected ester is essential for the chemoselective reductive-tautomerization of the nitrile.

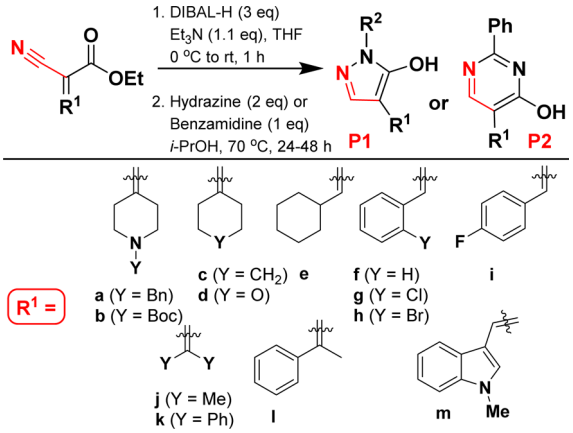
Scheme 3. Proposed Reductive Rearrangement Mechanism



Since the in situ protection/reduction is very fast under the reaction conditions, it was necessary to examine it at a lower temperature (−78 °C). One equivalent of DIBAL-H was quickly added with the ester disappearing almost immediately. This confirmed the in situ protection (**24b**). Warming to 0 °C followed by immediate addition of an additional 1.5−2 equiv of DIBAL-H (then stirred at ambient for 35 min) generates the imine salt (**24c**; 1609 cm^{-1}). Upon quenching, two new IR peaks (1678 and 1645 cm^{-1}) are seen which correspond to the regenerated ester and the conjugated enamine (**24d**). Liberation of hydrogen gas was confirmed through use of a colorimetric gas detection tube.[17] Based on those results, it seemed likely that the base might function catalytically. In fact, the reduction of compound **18** (analogue of **13**) with 20 mol % of Et_3N under the usual conditions resulted in complete conversion to the expected β-aminoacrylate. In addition, it seemed plausible that it might be possible to form the metal enolate through a conjugate reduction process.

Gratifyingly, it was found that treatment of α,β-unsaturated α-cyanoacetates with DIBAL-H (in the absence of amine) results in the formation of the same β-aminoacrylates generated from α-cyanoacetates containing an α-proton. Table 2 shows that many of the same substrates undergo conjugate reduction followed by reductive-tautomerization of the nitrile.

Table 2. Conjugate Reduction Chemistry[a]



reactant	R1 group	product(s)		isolated yield (%)	
		P1	P2	P1	P2
51	**a**	**64**	**27**	72	79
52	**b**		**65**		70
53	**c**	**29**	**30**	67	73
54	**d**	**66**	**67**	83	63
55	**e**	**31**	**32**	77	77
56	**f**	**38**	**39**	71	95
57	**g**	**68**	**69**	80	96
58	**h**	**40**	**41**	70	70
59	**i**	**70**		80	
60	**j**	**71**	**72**	88	72
61	**k**	**73**		75	
62	**l**	**74**		81	
63	**m**	**42**	**43**	70	86

[a]P1 N-substitution: R^2 = H, except for **64**, where R^2 = Ph.

Conversion to pyrazoles and pyrimdines was achieved under the same conditions used for the conversion of products from the reduction of the saturated cyanoacetates. The overall yields are as good or better than the saturated cyanoacetates. As an added benefit, the ability to use the unsaturated cyanoacetates may save a step as they are often precursors to the saturated compounds.

In addition to the increased efficiency of using the unsaturated cyanoacetate, it was observed that these β-

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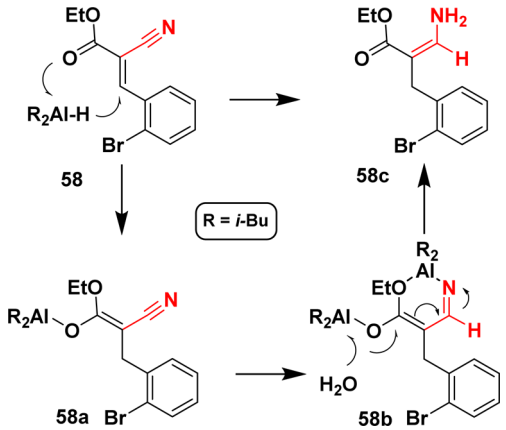
aminoacrylates were exclusively formed as the Z-isomer. None of the *E* isomer was detected by ^{1}H NMR. We speculate stereocontrol during enolate formation occurs via a conjugate olefin reduction with concomitant transfer of aluminum to the enolate oxygen (see Scheme 4). This would require a syn-

Scheme 4. Unsaturated Cyanoester Reduction Mechanism



coplanar arrangement of olefin and ester carbonyl. The aluminum atom of the aluminoimine would then be able to coordinate to the ethoxy oxygen to give an intermediate (**58b**) that would exclusively favor the *Z*-aminoester. This reduction reaction was also monitored using ReactIR, and an identical IR spectrum (with the exception of the differences between the saturated and unsaturated starting materials) was observed (see the Supporting Information).

In conclusion, we have developed a new chemoselective reductive-tautomerization of nitriles in α-cyanoesters and α-cyanoketones to prepare conjugated enaminoesters and ketones. This chemistry is made possible by formation of an oxoaluminum−enolate that protects the ester or ketone from reduction and is the driving force for rearrangement of the imine upon reaction quench. The scope of the methodology was expanded to include α,β-unsaturated-α-cyanoesters. The conjugated enamines that are produced can be efficiently converted to heterocycles, and this is an attractive alternative to current methods. Finally, we are actively engaged in expanding the synthetic utility of the intermediate β-aminoacrylates via their conversion to different classes of compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03285.

Experimental details, characterization of new compounds, and ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(13) The ratio of 7:1 was observed using a water quench and extractive workup. Upon switching to the quench method of Fieser (see below), the *Z*/*E* ratio was 57:1.

(14) The method of Fieser for quenching reactions using DIBAL-H is as follows: Cool the reaction in an ice/water bath and slowly add, in succession, 0.04*X* mL of water, 0.04*X* mL of 15 wt % aq NaOH solution, and 0.1*X* mL of water (*X* = mmol of DIBAL-H). Stir 30−60 min under cooling and then 30−60 min at ambient temperature. Dilute with THF as needed to facilitate stirring of the reaction. Add *Y* grams each of Celite and $MgSO_4$ (*Y* = grams of substate) and stir 30 min. Filter through Celite and wash filtrate with THF.

(15) The β-proton in the *Z* isomer typically appears around 6.4−6.8 ppm in the ^{1}H NMR. For the *E* isomer, the β-proton is observed ∼1 ppm downfield.

(16) For information on the use and applications of ReactIR, see: http://www.mt.com/gb/en/home/products/L1_AutochemProducts/ReactIR.tabs.documents.html.

(17) Gastec detector tube No. 30. For a review and instruction in use of colorimetric gas detection tubes, see: *Gastec Handbook: Environmental Analysis Technology*, 15th ed.; Gastec Corp.: Ayase City, 2014.

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