SYNLETT
Spotlight 254

Ethyl Diazoacetate (EDA)

Compiled by Gailing Liu

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

Ethyl diazoacetate (EDA), a typical alkyl diazoacetate, is an important, commercially available reagent in organic chemistry. It is a yellow liquid, stable below 5 °C, and can even be kept at ambient temperature for a few days in the absence of light. Early research with this reagent using light activation was not fruitful due to the high reactivity and low selectivity of the produced carbene intermediate in the subsequent reactions. However, in the presence of catalysts, EDA can be used as a versatile carbene precursor in chemical reactions including C–H, O–H, and N–H insertion reactions, and cyclopropanation of olefins in good selectivities. Due to the acidity of the α -H, EDA can also be used in aldol-type reactions.

Preparation

EDA can be conveniently prepared in high yield by adding an aqueous solution of NaNO_2 to a stirred mixture of an aqueous solution of ethyl glycinate hydrochloride and CH_2Cl_2 at $-5\text{ }^\circ\text{C}$,^{1a} or at room temperature.^{1b} It can also be prepared by other methods.²

Scheme 1

Abstracts

(A) The insertion of the $:\text{CHCO}_2\text{Et}$ moiety (formed from EDA) into the C–H bonds of cyclohexane or aldehydes yields the corresponding esters or ethyl β -ketoacetates.^{2,3,4}

(B) The TpXCu complexes (TpX = homoscorpionate ligands) efficiently catalyze the insertion of $:\text{CHCO}_2\text{Et}$ into the O–H bonds of saturated and unsaturated alcohols in high yields under mild conditions.⁵

(C) Iron(III) tetraphenylporphyrin chloride $[\text{Fe}(\text{TPP})\text{Cl}]$ can efficiently catalyze N–H insertion reactions of EDA with aliphatic and aromatic amines with yields ranging from 68% to 97%.⁶

(D) Reaction of EDA with electron-rich olefins affords cyclopropane-carboxylates in high yields. Copper, rhodium, and ruthenium compounds are the catalysts of choice.⁷ High diastereoselectivity and enantioselectivity have been achieved with careful selection of the catalyst. Recently, Pérez and co-workers reported that IPrCuCl catalyzes the transfer of :CHCO₂Et from EDA to unsaturated and saturated substrates (olefins, amines, alcohols) with very high yields. Interestingly, in the absence of substrate, IPrCuCl does not react with EDA to give the coupling products (fumarate and maleate).⁸

(E) Aziridines were obtained by the cycloaddition of imines with EDA. Aziridine moieties have been found in a number of biologically active products such as mitomycins and azinomycins.^{9,10}

(F) Ruthenium porphyrins catalyze the three-component coupling reaction of EDA with a series of *N*-benzylidene imines and alkenes to form functionalized pyrrolidines with excellent diastereoselectivity.¹¹

(G) A cycloheptatriene derivative was formed via the addition of :CHCO₂Et (derived from EDA) to an aromatic double bond in the presence of a catalyst and subsequent rearrangement of the bicyclic intermediate.¹²

(H) In the presence of (a) triphenylphosphine and catalytic amounts of iron(II) *meso*-tetra(*p*-tolyl)porphyrin or (b) sodium hydrosulfite and a catalytic amount of triphenylarsine and Fe(TCP)Cl, the reactions between EDA and aldehydes provide α,β -unsaturated esters in high yields with excellent stereoselectivities.¹³

(I) The direct aldol-type addition of EDA to aldehydes catalyzed by the chiral complex of BINOL derivatives and Zr(*O**t*-Bu)₄ gives α -diazo- β -hydroxy carbonyl compounds with moderate enantioselectivities (53–87% ee).¹⁴

(J) Palladium complexes catalyze the cross-coupling of EDA with aryl or vinyl iodides.¹⁵

References

- (1) (a) Searle, N. E. *Org. Synth., Coll. Vol.* **4** **1963**, 424.
(b) Wang, H. L.; Liu, G. L.; Li, Z. N.; Chen, H. L. *Chin. J. Fine Chem. Intermediates* **2008**, *38* (1), 40.
- (2) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley Interscience: New York, **1998**.
- (3) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043.
- (4) Caballero, A.; Díaz-Requejo, M. M.; Trofimenko, S.; Belderráin, T. R.; Pérez, P. J. *Eur. J. Inorg. Chem.* **2007**, 2848.
- (5) Morilla, M. E.; Molina, M. J.; Díaz-Requejo, M. M.; Belderráin, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *Organometallics* **2003**, *22*, 2914.
- (6) Baumann, L. K.; Mbuvi, H. M.; Du, G.; Woo, L. K. *Organometallics* **2007**, *26*, 3995.
- (7) Lloret, J.; Stern, M.; Estevan, F.; Sanaú, M.; Úbeda, M. A. *Organometallics* **2008**, *27*, 850.
- (8) Fructos, M. R.; Belderráin, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10846.
- (9) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612.
- (10) Zhu, Z. L.; Espenson, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 9901.
- (11) Li, G. Y.; Chen, J.; Yu, W. Y.; Hong, W.; Che, C. M. *Org. Lett.* **2003**, *5*, 2153.
- (12) Díaz-Requejo, M. M.; Pérez, P. J. *J. Org. Chem.* **2005**, *690*, 544.
- (13) (a) Mirafzal, G. A.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 176. (b) Cao, P.; Li, C. Y.; Kang, Y. B.; Xie, Z.; Sun, X. L.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 6628.
- (14) Yao, W.; Wang, J. *Org. Lett.* **2003**, *5*, 1527.
- (15) Peng, C.; Cheng, J.; Wang, J. *J. Am. Chem. Soc.* **2007**, *129*, 8708.