

SYNLETT
Spotlight 268Methyl Cyanoformate
(Mander's Reagent)

Compiled by Alex C. Bissember

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

Methyl cyanoformate, Mander's reagent (Figure 1), is most commonly employed to effect the regiocontrolled synthesis of β -keto esters through the C-acylation of pre-formed lithium enolates.^{1,2} It is superior to more traditional reagents such as acyl halides, anhydrides and carbon dioxide because these can also produce variable amounts of the corresponding O-acylated products.³ In addition to its aforementioned electrophilic behaviour, methyl cyanoformate has also been employed as a dipolarophile⁴ that reacts with an α -diazo- β -imido ester and, in the presence of polyoxotungstate, as a radical cyanating agent.⁵ Its homologue ethyl cyanoformate also behaves as a

dipolarophile⁶ and has been used to form substituted tetrazoles. It has also been employed in the preparation of α -keto esters.⁷

Methyl cyanoformate is a commercially available, colourless liquid that is readily prepared in small quantities (up to 30 g) by treating methyl chloroformate with potassium cyanide in the presence of a phase transfer catalyst such as 18-crown-6⁸ or tetra-*n*-butylammonium bromide.⁹

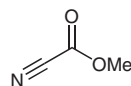
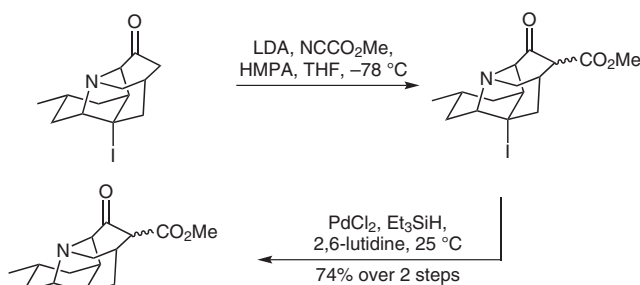


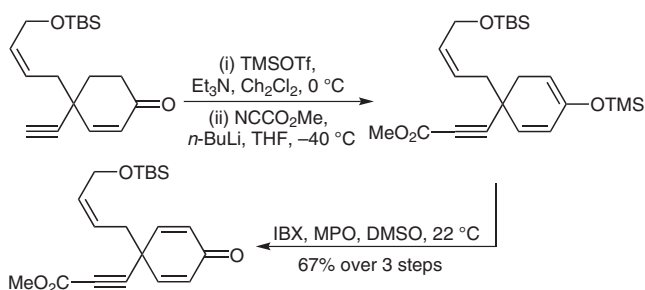
Figure 1 Methyl Cyanoformate

Abstracts

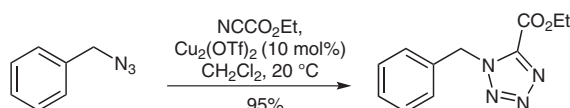
(A) Numerous syntheses of natural products and related compounds have featured the use of methyl cyanoformate to prepare β -keto esters. In the first total syntheses of (+)-lyconadin A and (–)-lyconadin B, Smith and co-workers¹⁰ employed Mander's reagent for precisely this purpose.



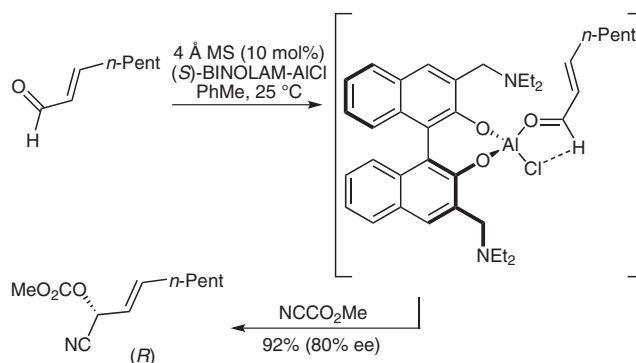
(B) The title reagent was used to prepare an acetylenic ester that served as an early stage intermediate in the first asymmetric total synthesis of (–)-platensimycin reported by Nicolaou and co-workers.¹¹



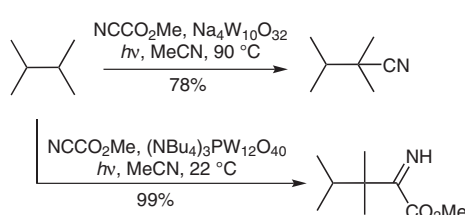
(C) Ethyl cyanofornate has been shown to engage in a copper(I)-catalyzed [3+2] dipolar cycloaddition with various organoazides, including benzylazide, to afford the corresponding 1,5-disubstituted tetrazoles.⁶



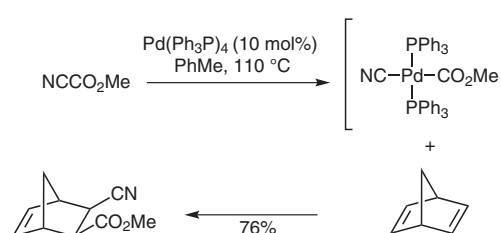
(D) Nájera and co-workers reported the one-step synthesis of various chiral cyanocarboxylates from a range of aldehydes using the title reagent in the presence of chiral bifunctional catalysts such as (*R*)- or (*S*)-BINOLAM-AlCl.^{12,13} It is believed that the catalytic cycle involves enantioselective hydrocyanation promoted by BINOLAM-AlCl, followed by the turnover-limiting O-alkoxycarbonylation step.



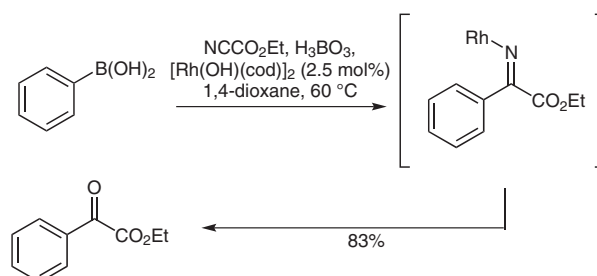
(E) Hill and Zheng have reported that irradiation ($\lambda > 280$ nm) of mixtures of various alkanes and methyl cyanofornate in the presence of either $W_{10}O_{32}^{4-}$ or $PW_{12}O_{40}^{3-}$ produces the corresponding nitrile or α -iminoester, respectively.⁵ Such reactions can be highly selective if proper temperature controls are applied. An iminyl radical intermediate is thought to be involved in these conversions.



(F) Nishihara and co-workers have described the highly stereoselective and palladium-catalyzed addition of methyl cyanofornate across norbornene-type double bonds and so affording norbornanes bearing both cyano and ester groups.¹⁴ It is believed that the complex *trans*-Pd(CN)(CO₂Me)(Ph₃P)₂ is an intermediate in the catalytic cycle associated with this cyanoesterification process.¹⁵



(G) Shimizu and Murakami have effected the selective formation of α -keto esters by the rhodium-catalyzed reaction of ethyl cyanofornate with arylboronic acids.⁷ The observed conversion arises through preferential addition of an intermediate rhodium(I) species to the cyano group rather than to the ester carbonyl group. This conversion stands in sharp contrast to the outcomes observed when ethyl cyanofornate reacts with either phenyllithium or phenylmagnesium bromide so as to afford ethyl benzoate.⁷



References

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