Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Cyanomethyl Esters: Useful Protection for Carboxylic Acids

Helmut M. Hugel [a], K. Vijaya Bhaskai [b] & Robert W. Longmore [b]

[a] Department of Applied Chemistry, Phillip Institute of Technology, Plenty Road, Bundoora, Victoria, 3083

[b] Research School of Chemistry, Australian National University, Canberra, A. C. T., 2601, Australia

Published online: 23 Sep 2006.

To cite this article: Helmut M. Hugel , K. Vijaya Bhaskai & Robert W. Longmore (1992) Cyanomethyl Esters: Useful Protection for Carboxylic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:5, 693-697, DOI: 10.1080/00397919208019271

To link to this article: http://dx.doi.org/10.1080/00397919208019271

SYNTHETIC COMMUNICATIONS, 22(5), 693-697 (1992)

# CYANOMETHYL ESTERS: USEFUL PROTECTION FOR CARBOXYLIC ACIDS

Helmut M. Hugel[a*], K. Vijaya Bhaskar[b] and Robert W. Longmore[b]

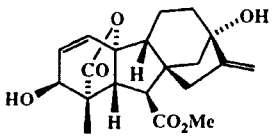
[a]Department of Applied Chemistry, Phillip Institute of Technology, Plenty Road, Bundoora, Victoria 3083. [b]Research School of Chemistry, Australian National University, Canberra, A.C.T. 2601, Australia



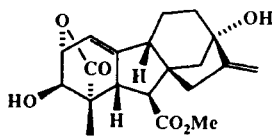
**Abstract :** The alkylation of carboxylate salts with chloroacetonitrile yields cyanomethyl esters. Deprotection of the carboxyl group is most readily performed by stirring with an aqueous solution of sodium sulfide.

For many years we have grappled with the task of protecting the B-ring carboxyl group in gibberellins.[1] Because of the sterically hindered environment, the vigorous conditions required to hydrolyse simple alkyl esters by the standard $B_{AC}2$ route, are likely to result in unwanted reactions in the rest of the molecule. Methyl gibberellate (**1**), for example, is rapidly isomerised to the isolactone **2** in 0.01M NaOH.[2] Methyl esters may be cleaved with iodide ion[3] or thiolates[4] in dipolar aprotic solvents, but outcomes are still often unsatisfactory. Benzyl or *tert.*-butyl

*Author to whom enquiries should be addressed



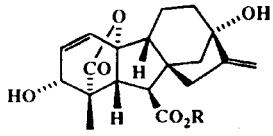

1



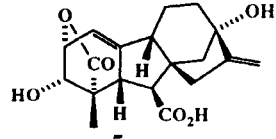

2

groups cannot be removed in the presence of the exocyclic methylene group which is an integral part of most natural gibberellins,[5] and even the conditions required for the removal of more labile groups, *e.g.* 4-methoxybenzyl, methoxymethyl, SEM, phenacyl, trichloroethyl, may be incompatible with the more labile GAs such as **1**.[6]

In a recent attempt to prepare 3-epi-gibberellic acid (**3**), a compound required for a current biological project, we had prepared the methoxymethyl ester (**4**) of this compound by sodium borohydride reduction of the 3-ketone,[7] but were surprised to find that **4** was even more acid-sensitive than methyl gibberellate (**1**), a compound well known for its lability towards a wide range of reagents. When hydrolysis was carried out under standard conditions (methanol plus 1-2 drops of trimethyl silyl chloride), only the isomeric lactone **5** was obtained.




**3** R= H
**4** R = $CH_2OMe$

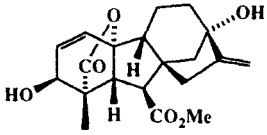


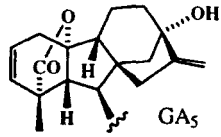
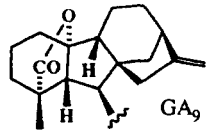
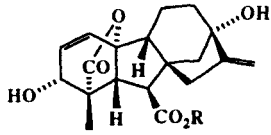

**5**

Following an extensive search for a more suitable protecting function, we have discovered that cyanomethyl esters are sufficiently stable to a reasonable range of reaction conditions, but may be readily removed under mildly basic conditions. Moreover, they may be easily prepared directly from the carboxylic acids in high yields without prior activation. Cyanomethyl esters of protected amino acids have previously been used as activated carboxyl components for aminolysis reactions in

**Table : Formation and hydrolysis of cyanomethyl esters**

$$RCO_2H \underset{Na_2S,\ H_2O\text{-acetone}}{\overset{ClCH_2CN,\ Et_3N}{\rightleftharpoons}} RCO_2CH_2CN$$

| R = | YIELD (%) Ester | Acid |
|---|---|---|
| $C_6H_5$- | 96 | 90 |
| 2-Cl-$C_6H_4$- | 87 | 70 |
| $C_6H_5CH_2$- | 92 | 79 |
| *trans*-$C_6H_5CH{=}CH$- | 91 | 70 |
|  | 78 | 74 |

| | YIELD(%) Ester | Acid |
|---|---|---|
|  GA$_5$ | 90 | 80 |
|  GA$_9$ | 89 | 80 |
|  | 80 | 75 |

the synthesis of peptide derivatives,[8] but they seem to have found little use in a protecting role. We have determined that cyanomethyl esters are only marginally less stable than simple methyl esters towards many nucleophiles, and yet may be readily removed with the "soft base", $Na_2S$, in aqueous acetone, or more slowly with a $K_2CO_3$-$KHCO_3$ mixture in aqueous THF.[9] Cyanomethyl esters are moderately stable in acidic media and will withstand lithium *tert.*-butoxide or potassium carbonate in isopropyl alcohol. They are rapidly trans-esterified in mixtures of potassium carbonate and methanol or ethanol, however. A range of examples is given in the table.

The simple gibberellin examples are especially noteworthy, since normal base-catalysed hydrolysis of these compounds requires several hours reflux in 20% KOH-MeOH. The successful hydrolysis of the cyanomethyl esters of gibberellic

and 3-epi-gibberellic acids, however, provides an ultimate test of the methodology. It is especially suited to sterically hindered carboxyl functions and should be generally useful for the manipulation of other sensitive natural products containing such groups.

## EXPERIMENTAL SECTION

**Cyanomethyl ester preparation**. To the carboxylic acid (1 equiv.) dissolved in dichloromethane and triethylamine (2 equiv.) was added chloroacetonitrile (1-2 equiv.), and the reaction mixture stirred at room temperature. TLC was used to monitor the progress of reaction. For insoluble substrates like gibberellic acid, it was necessary to heat the solution at reflux for 24h. Upon completion of the reaction, the triethylamine salt was filtered off under vacuum, further dichloromethane added and the solution successively washed with aqueous sodium carbonate, 2M HCl solution, and then distilled water. The organic phase was then dried ($MgSO_4$) and concentrated in vacuo to afford the ester. The cyanomethyl esters were characterised spectroscopically with a peak at $\delta$4.8 ($CO_2CH_2C{\equiv}N$) in $^1H$ NMR spectra being particularly diagnostic.

**Ester deprotection.** Method (a) A mixture of cyanomethyl ester (1 equiv.) in 10 ml acetone-water (1:1) was stirred at room temperature and then treated with an aqueous solution of $Na_2S.9H_2O$ (1 equiv.). TLC indicated that hydrolysis was complete in 30 minutes. The reaction mixture was acidified with 2M HCl, the acetone removed in vacuo and the product extracted into ethyl acetate or diethyl ether. The organic extract was washed with brine ($MgSO_4$) and the solvent evaporated to afford the acid which was identified by direct comparison with authentic samples. Method (b) Potassium carbonate (1.08g, 7.8mmol) and potassium bicarbonate (0.26g, 2.6mmol) were added to a stirred solution of the cyanomethyl ester derived from **3** (500mg, 1.3mmol) in acetone -water (40ml 1:1).

After 48h at ambient temperature, the reaction mixture was diluted with ethyl acetate (20ml) and acidified carefully with 1M HCl to pH 4. Extraction with ethyl acetate-n-butanol (2:1) afforded 3-epigibberellic acid (**3**) in 75% yield.

**Acknowledgement:** The authors thank Professor L.N. Mander for helpful discussions and P. Laming for running some nmr spectra.



## REFERENCES AND NOTES

1. Mander, L.N. Nat. Product Reports, 1988, 5, 541.
2. Kirkwood, P.S., MacMillan, J. and Sinnot, M.L. J. Chem. Soc. Perkin Trans I, 1980, 2117.
3. Nagata, W., Wakabayashi, T., Narisada, M., Hayase, Y. and Kumata, S. J. Am. Chem. Soc., 1971, 103, 5740.
4. Bartlett, P.A. and Johnson, W.S. Tetrahedron Lett., 1970, 4459. Yamaguchi, I., Takahashi, N. and Fujita, K. J. Chem. Soc., Perkin Trans. 1, 1975, 992.
5. Hydrogenolysis is obviously not feasible, while the double bond readily migrates into the endocyclic position in anhydrous acidic media or is hydrated in aqueous acid.
6. Green, T.W. "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc., New York 1981.
   Haslam E., "Protective Groups in Organic Chemistry," J.F.W. McOmie ed., Plenum press, London, 1973.
7. Serebryakov, E.P. Z. Chem. ,1977, 17, 372.
8. Stewart, F.H.C. Aust. J. Chem., 1970, 23, 2147.
9. A further method for hydrolysis is to heat the cyanomethyl esters with N-bromosuccinimide (1.2 equiv.) in $CCl_4$-$CH_2Cl_2$ at reflux for 2 hours, followed by warming with $H_2O$. This method is not compatible with the gibberellin molecule, however.

(Received in UK 16 September, 1991)