Prop-2-ynyl as a protective group for carboxylic acids: a mild method for the highly selective deprotection of prop-2-ynyl esters using tetrathiomolybdate

Palanichamy Ilankumaran, N. Manoj and Srinivasan Chandrasekaran*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

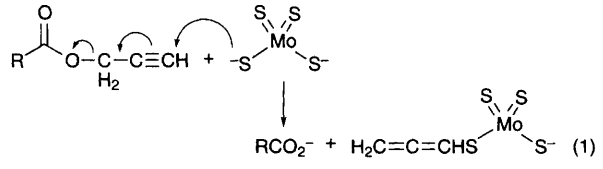
It is shown that prop-2-ynyl esters are useful protecting groups for carboxylic acids and that they are selectively deprotected in the presence of other esters on treatment with tetrathiomolybdate under mild conditions.

There is a constant search for new, easy to introduce and selectively removable protecting groups in organic synthesis. Over the years a number of protective groups have been developed for carboxylic acids[1] of which esterification offers several advantages because of its easy preparation and stability towards several reagents. However, selective cleavage of one type of ester in the presence of another ester(s) is by no means a trivial problem which is routinely encountered in peptide synthesis. Even though several procedures are currently available for this purpose, difficulties still exist.

Earlier work from our laboratories has shown that benzyltriethylammonium tetrathiomolybdate $[PhCH_2NEt_3]_2MoS_4$ **1** is a useful sulfur transfer reagent in organic synthesis[2] as well as a reagent that can mediate reductive dimerization of organic thiocyanates[3] and alkyl azides.[4] In exploring further the utility of the induced internal redox reaction of tetrathiomolybdate **1** in organic synthesis and to find out whether **1** can be used as a reagent for reduction of the acetylenic bond, prop-2-ynyl benzoate was treated with **1** in acetonitrile. Surprisingly, it was found that it led to the cleavage of the ester resulting in the formation of benzoic acid as the only isolable organic product (85%). This prompted us to study the behaviour of carboxylic prop-2-ynyl esters with tetrathiomolybdate **1**. We present the results of this investigation in this communication.

Treatment of a number of prop-2-ynyl esters with tetrathiomolybdate **1** (2 equiv., 25 °C 12–41 h) in acetonitrile led to the formation of the carboxylic acids in high yields (61–97%).† Our results indicate that carboxylic prop-2-ynyl esters are unique in that they undergo selective deprotection on treatment with **1** in the presence of a number of other types of esters. The results are summerized in Table 1. As can be seen the prop-2-ynyl ester is selectively deprotected in high yield in the presence of acetate (entry 3). The unusually selective deprotection of prop-2-ynyl ester in the presence of benzyl ester (entry 5) and *tert*-butyl ester (entry 6) are noteworthy. A special mention must be made of the high selectivity achieved in the deprotection of prop-2-ynyl ester in the presence of allyl ester. Normally allyl and prop-2-ynyl esters are deprotected on treatment with Pd^{2+} species[5] or cobalt carbonyl.[6] Guibe has demonstrated that allyl ester can be deprotected in the presence of prop-2-ynyl ester using Pd^{2+}/Bu_3SnH.[7] The present deprotection methodology offers an alternate selectivity in the presence of allyl esters (entry 4). The mildness of the present method is illustrated in the example of a successful deprotection of prop-2-ynyl ester of penicillin G (entry 8) which has a sensitive β-lactam unit. In the selective deprotection of prop-2-ynyl ester derived from phenyl alanine with **1** (entry 7), *N*-benzoyl phenyl alanine was obtained in excellent yield.

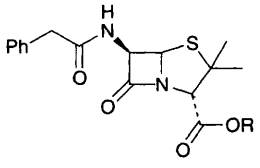
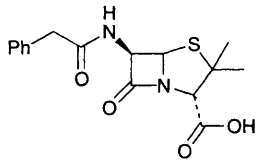
At this stage the mechanism of this selective deprotection with **1** remains unclear. However, it is possible to speculate a pathway involving nucleophilic attack of the sulfur anion in **1** on the terminal carbon of the triple bond followed by cleavage of the carbon–oxygen bond to give the carboxylic acid [eqn. (1)].



(1)

This is partly supported by the observation that homo prop-2-ynylic ester (entry 9) on treatment with **1** under similar

Table 1 Selective deprotection of prop-2-ynyl esters with tetrathiomolybdate **1**

Entry	Substrate[a]	Product[b]	*t*/h	Yield[c] (%)
1	PhCOOR	$PhCO_2H$	12	85
2	$Me[CH_2]_6COOR$	$Me[CH_2]_6CO_2H$	24	82
3	$PhCH(OCOMe)CO_2R$	$PhCH(OCOMe)CO_2H$	23	93
4	*o*-CH_2=$CHCH_2O_2CC_6H_4CO_2R$	*o*-CH_2=$CHCH_2O_2CC_6H_4CO_2H$	20	97
5	*o*-$PhCH_2O_2CC_6H_4CO_2R$	*o*-$PhCH_2O_2CC_6H_4CO_2H$	16	80
6	*o*-$Bu^tO_2CC_6H_4CO_2R$	*o*-$Bu^tO_2CC_6H_4CO_2H$	48	83
7	$PhCH_2CH(NHCOPh)CO_2R$	$PhCH_2CH(NHCOPh)CO_2H$	39	93
8			48	61
9	$PhCO_2(CH_2)_4C$≡CH	No reaction	48	—

[a] R = CH_2C≡CH; All the prop-2-ynyl esters were prepared from the carboxylic acids and prop-2-ynyl alcohol in the presence of DCC and DMAP. [b] All the products gave satisfactory spectral data. [c] Yields refer to purified isolated products.

conditions remains unaffected. Further work is necessary to delineate the mechanism of the reaction.

Since the present methodology works with high efficiency under practically neutral conditions and without recemization‡ this protection and deprotection of carboxylic acids involving prop-2-ynyl esters is likely to have good potential in peptide synthesis.

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Footnotes

† *General procedure*: To a stirred solution of prop-2-ynyl ester (2 mmol) in MeCN (8 ml), tetrathiomolybdate **1** (2 mmol) was added. After stirring for 6 h at 25 °C a further 1 equiv. of **1** (2 mmol) was added. After completion of the reaction (TLC) a few drops of 2 mol dm^{-3} HCl was added to neutralise the reaction mixture and the solvent was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2–Et_2O (1 : 5, 50 ml) and the solvent was removed to reveal the crude product which was purified.

‡ Based on the optical rotation of *N*-benzoyl phenyl alanine reported in the literature.[8]

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