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A Very Useful and Mild Method for the Protection and Deprotection of Carboxylic Acids

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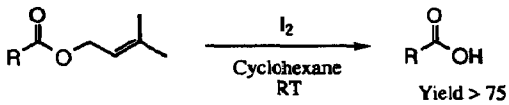
Key words: *Protection, deprotection, 3-methylbut-2-enoate carboxylic acid, iodine.*

Abstract: *3-Methylbut-2-enoate carboxylic acid can be a good protecting group of carboxylic acids and can be removed easily by using iodine in cyclohexane at room temperature.*

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been and are being developed for this purpose.

Carboxylic acid can be protected as anhydrides [1], amides [2] or esters [3]. Unsaturated esters are particularly useful as protecting groups. Allyl esters which are formed by condensing the acid with allyl bromide in basic conditions [4], can be cleaved by using $Pd(OAc)_2$ [5], $Pd(Ph_3P)_4$ [6], $PdCl_2(Ph_3P)_2$ [7], $(Ph_3P)_3RhCl$ [8] or Me_2CuLi [9]. The 3-buten-1-yl ester synthetized by condensing the alcohol with the acid can be removed by using ozone followed by the addition of triethylamine or DBU [10]. The 4-(trimethylsilyl)-2-buten-1-yl and the α-methylcinnamyl groups have also been used as protecting groups of acid functionalities. These protecting groups can be removed by using respectively $Pd(Ph_3P)_4$ [11] and $Me_2Sn(SMe)_2$ in acidic conditions [10]. In each case, the regeneration of the acid from the unsatured ester involves metals, acidic or basic conditions which can be incompatible with other functionalities.

We would like to report here the protection of acid by 3-methylbut-2-enol, to give an ester which can be cleaved in very mild and neutral conditions using iodine in cyclohexane.



Yield > 75 %

Our results are summarised in the Table . The synthesis of the esters **1** - **7** was realized by using two methods. One involves a methyl ester interchange with 3-methylbut-2-enol by using a catalytic amount of dimethylaminopyridine (DMAP) (compounds **1** and **2**) [12] or by using a catalytic amount of *p*-toluenesulfonic acid (compounds **3** and **4**). The second method involves the esterification of the acid by 3-methylbut-2-enol by using dicyclohexylcarbodiimide (DCC) in the presence of DMAP (compounds **5** - **8**) [13].

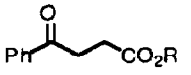
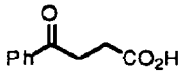
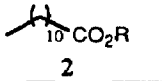
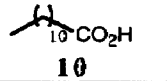
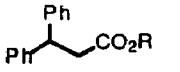
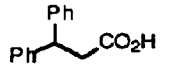
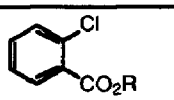
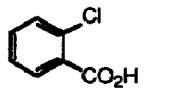
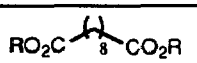
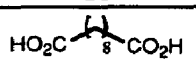
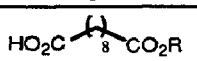
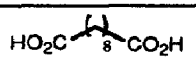
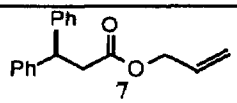
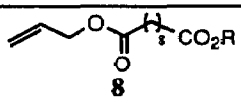
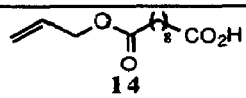
Treatment of the esters **1** - **8** in cyclohexane (0.1 M) by 1.5 equiv of iodine for 6 hours allows the isolation of the corresponding acid with a yield higher than 75 %. For compounds **5** and **6**, the reaction was performed with 3 equivalents of iodine for 24 hours.

Deprotection of the diester **8**, which contained an α-unsaturated carboxylate moiety, was chemoselective, giving **14** exclusively in 85 % yield. Furthermore, no acid was detected after 4 days on treating the allylic ester **7** with iodine.

Work is underway in our laboratory to delimit the synthetic application of our discovery and to approach a mechanistic understanding of it.

General Procedure. Iodine (1.5 equiv) was added to a solution of the appropriate ester (see Table) in cyclohexane (0.1 M). After vigourously stirring at room temperature for 6 hours, the solution was diluted by dichloromethane.The organic layer was washed with a satured aqueous Na_2CO_3 solution. The aqueous layer was then acidified by 6N HCl and extracted with dichloromethane. The combined organic layers were washed with water, dried over $MgSO_4$ and then evaporated to give the corresponding carboxylic acid.

Table: Deprotection of esters by iodine

Ester [a]	Acid	Yield (%)
 **1**	 **9**	75
 **2**	 **10**	97
 **3**	 **11**	94
 **4**	 **12**	84
 **5**	 **13**	90
 **6**	 **13**	90
 **7**	–	0 [b]
 **8**	 **14**	85

a) R = 3-Methylbut-2-enyl b) Starting material recovered quantitatively

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