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One-pot tethering of organic molecules through non-symmetric malonate derivatives

Daniel Sherman, Rimma Shelkov and Artem Melman*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

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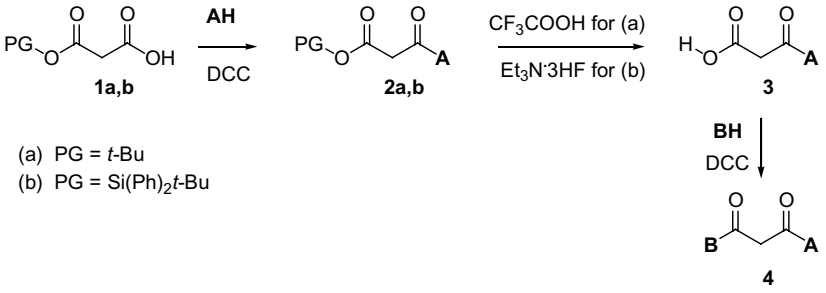
Abstract—A new method for one-pot chemoselective heterobifunctional cross-linking of organic molecules is described. The method is based on *tert*-butyldiphenylsilyl malonate and involves two sequential carbodiimide couplings with two different molecules possessing a hydroxy or an amino functionality with one intermediate one-pot fluoride deprotection.

Heterobifunctional cross-linking of organic molecules has found an extensive use in solid phase synthesis, preparation of prodrugs, targeted delivery of biologically active compounds and many others applications.[1,2] While a variety of different cross-linkers has been proposed, the most commonly used method of permanent tethering relies on the formation of amide bonds between amino or carboxylic groups.[2] Organic compounds possessing other functions such as hydroxyls are substantially less reactive than amines and their acylation is often complicated, especially if substrates are sterically hindered.[3] Elaboration of a methodology that is capable of efficient covalent tethering of substrates possessing hydroxy groups (including sterically hindered ones) in high yields and chemoselectively under mild reaction conditions is therefore of substantial interest.

Recently we reported a new, highly efficient acylation of sterically hindered alcohols through the reaction with carboxylic acids, which can form ketenes upon treatment with carbodiimides.[4] Here we report on a new method for the permanent tethering of two organic units possessing hydroxy or amino functionalities using the acylation of these groups through ketene intermediates produced from malonic acid monoesters.

Homobifunctional cross-linking of two identical molecules possessing hydroxy or amino groups using this reaction can be done in a straightforward way using a direct esterification of malonic acid with 2 equiv of an alcohol and a carbodiimide.[5] Acylation through ketene intermediates can also be applied for much more synthetically important heterobifunctional tethering of



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* Corresponding author. Tel.: +972 2658 5279; fax: +972 2658 5345; e-mail: amelman@chem.ch.huji.ac.il

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two different units **AH** and **BH** using monoprotected malonic acid derivatives of type **1**. Such a procedure should involve first a carbodiimide-mediated coupling of substrate **AH** with a monoprotected malonate of type **1** followed by deprotection of a diester of type **2** and second a carbodiimide coupling between the resulting monoester **3** and substrate **BH** to afford the desired non-symmetrical diester of type **4**.

Since the removal of a *tert*-butyl group can be done easily in the presence of other esters, mono-*tert*-butyl malonate could be used for implementing this approach[6,7] although the conditions of acid-catalyzed deprotection are too harsh for the majority of polyfunctional substrates. Other protecting groups for malonic acid also require the use of strongly acidic or basic reagents for their removal (e.g., methoxybenzyl or 9-fluorenylmethyl esters) or are difficult to implement in small scale reactions (e.g., catalytic hydrogenation or electrolysis).

Silicon-based protecting groups for alcohols have found extensive use in organic synthesis due to the ease of their selective removal by fluoride anions.[8] In contrast, protection of a carboxyl group as a silyl ester is much less common due to their very high reactivity towards nucleophilic reagents. However, after the attempted synthesis of different silyl malonates we found that *tert*-butyldiphenylsilyl malonate can be isolated as a reasonably stable crystalline solid.[9]

Like other malonate monoesters, a carbodiimide-mediated coupling of *tert*-butyldiphenylsilyl malonate with alcohols and amines proceeded in practically quantitative yields under very mild conditions. The subsequent removal of the *tert*-butyldiphenylsilyl ester protecting group from **2** can be done easily with commercially available tetra-*n*-butylammonium fluoride. However, all commercially available sources of Bu_4NF contain at least 3 equiv of water and attempts to produce dry Bu_4NF result in a highly basic reagent that is prone to decomposition.[10] After searching for alternative fluoride anion sources, we found that equimolar amounts of commercially available anhydrous and neutral triethylamine–hydrogen fluoride complex $Et_3N{\cdot}3HF$ easily deprotects silyl malonates of type **2** thus providing malonate monoesters of type **3**.

We found that residual triethylamine–hydrogen fluoride does not interfere with the subsequent carbodiimide coupling. This fact made it possible to conduct the second carbodiimide-mediated coupling of malonate monoesters of type **3** with **BH** in one pot without any intermediate purification. The final purification of the resultant non-symmetric malonates of type **4** was achieved by flash chromatography. No appreciable amounts of symmetrical malonate diesters such as $(AOCO)_2CH_2$ or $(BOCO)_2CH_2$ were detected in the reaction. The simplicity of the method is demonstrated by the representative procedure that could also be suitable for the preparation of combinatorial libraries.[11]

The examples in Table 1 demonstrate the versatility of this method. Alcohols, including sterically hindered ones, provided non-symmetrical malonates of type **4** in good to excellent non-optimized yields.

Table 1. Isolated yield of non-symmetrical malonates of type **4** after three stages

Entry	Molecule **AH**	Molecule **BH**	Isolated yield, %
a	Geraniol	*tert*-BuOH	91
b	Geraniol	Diacetone-D-glucose	84
c	Benzhydrol	Geraniol	78
d	Geraniol	Adamantol	80
e	(−)-Menthol	4-Hydroxybenzyl alcohol	74
f	Adamantol	Mercaptoethanol	68
g	Mercaptoethanol	2,3-Isopropylidene glycerol	55
h	2-Phenyl-2-propanol	Diisopropylamine	56
i	Octanol	4-aminophenol	49 + 26

Reactions with polyfunctional substrates (entries e–g) demonstrate the chemoselectivity of the method. In all these entries the acylation selectively proceeded on the aliphatic hydroxy group and no appreciable amounts of acylation of thiol or phenol functionalities were detected. It should be mentioned that these chemoselectivities are completely opposite to conventional carbodiimide esterifications.[12] Formation of the malonamide linkage by the current procedure was somewhat slow and only moderate yields were achieved (entry h). Reaction with 4-aminophenol was the only case where low chemoselectivity was observed thus providing mainly products of N-acylation (49%) with a substantial amount of the O-acylation product (26%).

In conclusion, one-pot permanent tethering through unsymmetric malonate derivatives provide a number of important advantages versus existing methods including the possibility to conjugate sterically hindered hydroxy and amino groups, short reaction times, equimolecular amounts of tethering reagents and the absence of laborious intermediate purification stages.

Acknowledgements

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9. To a solution of malonic acid (3.03 g, 29.1 mmol) and triethylamine (2.95 g, 29.1 mmol) in CH_2Cl_2 (20 mL) was added *tert*-butylchlorodiphenylsilane (4.0 g, 14.6 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was evaporated and dissolved in ethyl acetate–petroleum ether 1:1 mixture (100 mL), washed with cold water (3 × 50 mL), dried over Na_2SO_4 and evaporated. The residue was dissolved in EtOAc (5 mL), diluted with 100 mL of petroleum ether and kept at −34 °C overnight to crystallize to afford mono-*tert*-butyl diphenylsilyl malonate (2.0 g, 5.54 mmol, 38%). This product is a crystalline solid stable for weeks at −18 °C and may be purified by recrystallization from ethyl acetate–petroleum ether.
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11. To a solution of geraniol in (1 mL of a 1 M solution in dichloromethane) was added a solution of *tert*-butyldiphenylsilylmalonate **1a** (1 mmol of a 1 M solution in dichloromethane) and a solution of DCC (1 mmol of a 1 M solution in dichloromethane). The reaction mixture was stirred for 10 min and a solution of $Et_3N{\cdot}3HF$ complex (1 mmol of a 1 M solution in dichloromethane) was added. The reaction mixture was stirred for 10 min and a solution of *t*-BuOH (1 mmol of a 1 M solution in dichloromethane) and a solution of DCC (1 mmol of a 1 M solution in dichloromethane) were added. The reaction mixture was stirred for 10 min, filtered and evaporated. The residue was purified by flash chromatography (0–10% EtOAc–petrol mixture) to give the corresponding non-symmetric malonate **4a** (1.17 g, 91%).
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