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Synthesis of Monosubstituted 1,1-Dicarbonyl Ester 1,3-Dienes

Olivier Rousseau, Thierry Delaunay, Raphaël Robiette*

Institute of Condensed Matter and Nanosciences, Université catholique de Louvain, Place Louis Pasteur 1, L4.01.02, 1348 Louvain-la-Neuve, Belgium
Fax +32(0)10474168; E-mail: raphael.robiette@uclouvain.be

Received: 02.11.2013; Accepted after revision: 23.11.2013

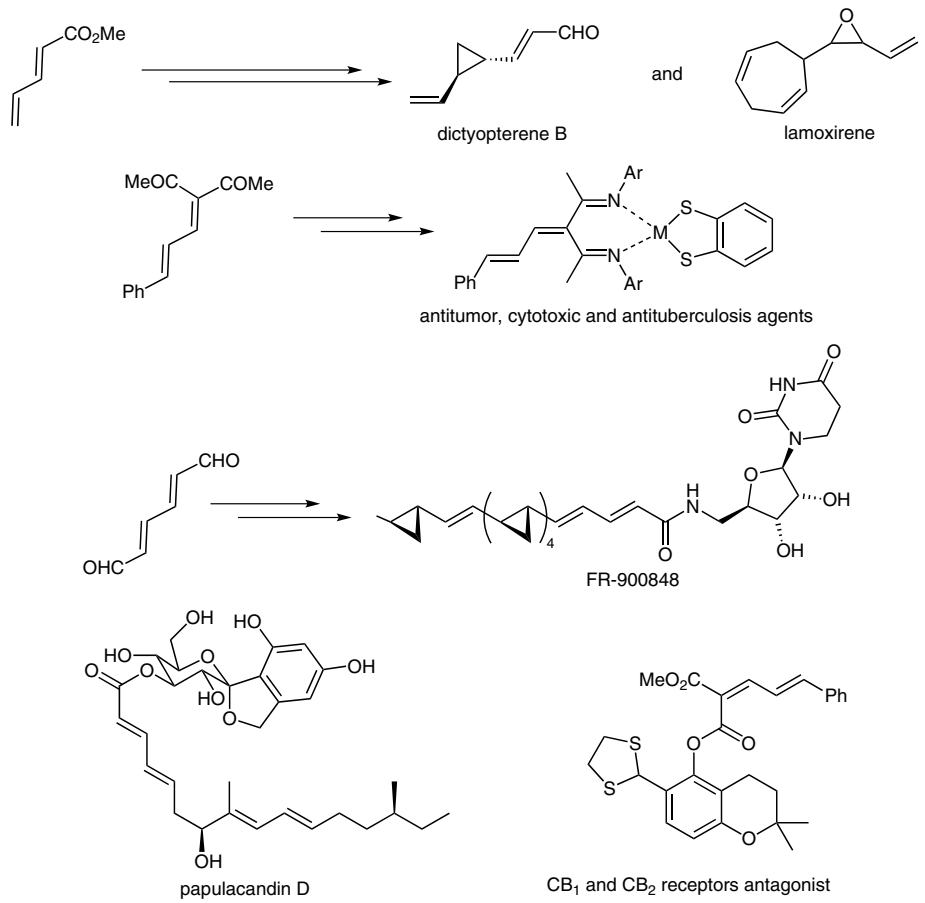
Abstract: The synthesis of various electron-deficient 1,1-dicarbonyl ester 1,3-dienes substituted in position 2 or 3 of the diene moiety has been developed.

Keywords: bromine, condensation, cross-coupling, 1,3-dienes, malonates

Electron-poor 1,3-dienes are versatile building blocks in organic chemistry which have been reported as key intermediates in the syntheses of a series of therapeutically important targets (Scheme 1).[1] Several biologically active (natural and non-natural) compounds have also been found to include such a structural motif.[2]

From a synthetic point of view, the interest of these intermediates relies mainly on their high reactivity and the diversity of reactions in which they can be involved: (4+2),[3] (3+2)[4] and (2+1)[1a,5] cycloadditions, Michael additions,[6] cross-metathesis reactions,[7] Morita–Baylis–Hillman reactions,[8] polymerization reactions.[9]

If the preparation of dienyl ester compounds is well documented,[10,11] there are, in contrast, fewer reports on the synthesis of their bis-activated analogues, the 1,1-dicarbonyl 1,3-dienes.[11,12] In particular, derivatives not substituted in position 4 of the diene moiety are scarcely described.[13] This may probably be accounted for by the high reactivity of these species which imposes the use of



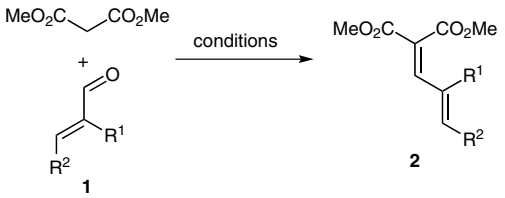
Scheme 1

SYNLETT 2014, 25, 0519–0522
Advanced online publication: 20.12.2013
DOI: 10.1055/s-0033-1340468; Art ID: ST-2013-D1027-L

mild reaction conditions for their preparation. Herein, we report the synthesis of 2- and 3-substituted 1,1-dicarbonyl ester 1,3-dienes from dialkyl malonates.

The most efficient route toward non- and 4-substituted 1,1-dicarbonyl ester 1,3-dienes is the Knoevenagel condensation between malonate and acrolein derivatives. Several basic conditions have been reported for this reaction (Table 1).[12] However, application of these reaction conditions to the synthesis of 1,1-dicarbonyl 1,3-dienes substituted in position 3 of the diene ($R^1 \neq H$), i.e. using α-substituted acrolein derivatives, led to no or poor conversions. We thus took inspiration in reaction conditions reported for the Knoevenagel condensation of aromatic aldehydes and considered the use of a Lewis acid. In the event, we found that the use of $TiCl_4$[14] allows the synthesis of 1,1-dicarbonyl 1,3-dienes substituted in position 3 of the diene ($R^1 \neq H$).[15] Even sterically hindered 2-phenylacrolein reacts with dimethyl malonate in these conditions, although in low isolated yield.

Table 1 Knoevenagel Condensation between Malonate and Acrolein Derivatives

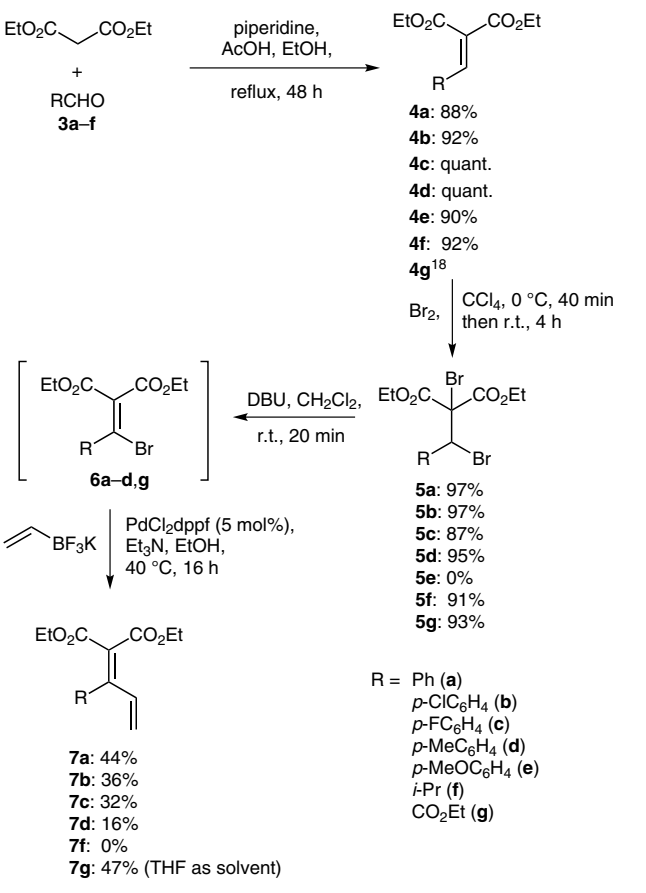


R^1	R^2	Conditions	Yield (%)[a]	Ref.
H	H	LiBr, Ac_2O, 80 °C	87	12h
H	Ph	L-lysine, DMSO, r.t.	97	12c
		piperidine, CH_2Cl_2, r.t.	62	12b
Me	H	$TiCl_4$, THF, r.t.	77	this work
Ph	H	$TiCl_4$, THF, reflux	34	this work

[a] Yield of isolated compound after flash chromatography.

Unfortunately, every attempt to apply this direct Knoevenagel strategy to 2-substituted diene derivatives by reaction of α,β-unsaturated ketones failed. This can probably be explained by the lower reactivity of ketones, as compared to aldehydes, and/or by the reversibility of the initial addition.[16] We thus have developed new methodologies to access 2-substituted 1,1-dicarbonyl ester 1,3-dienes.

Our strategy toward 2-substituted derivatives is based on the preparation of vinylic compounds by Knoevenagel condensation onto aromatic or alkyl aldehydes, followed by halogenation and direct Suzuki coupling to install the second carbon–carbon double bond of the 1,3-diene moiety (Scheme 2). The first step, the Knoevenagel reaction of diethyl malonate with aldehydes, provides vinylic compounds **4a**–**f** in excellent yields, with both electron-poor and electron-rich aromatic aldehydes[17] as well as aliphatic ones[6a] (**4g** was prepared according to a reported procedure[18]). Olefin dibromination was then performed in the presence of bromine to give **5a**–**d**,**f**,**g** in excellent yields (formation of **5e** could not be observed). Upon addition of a non-nucleophilic base, **5a**–**d**,**f**–**g** underwent elimination to afford the halogen Suzuki partners **6a**–**d**,**g**. In the case of **5f** bearing an alkyl substituent, elimination product (**6f**) could not be observed with the main product being the corresponding retro-dibromination product **4f**. All our attempts (change of solvent, base, temperature, additives, etc.) to obtain **6f** as the main product failed. This observation as well as the failure of the dibromination of **4e** can probably be accounted for by the increased lability of the CH–Br bond due to the electron-donating character of R in these cases.

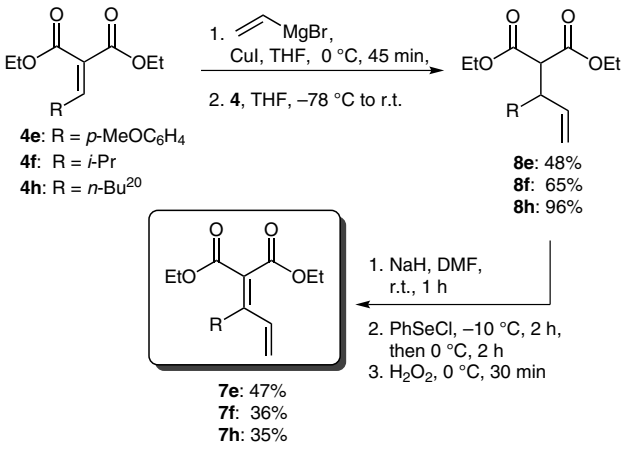


Scheme 2 Syntheses of 2-substituted 1,1-dicarbonyl ester 1,3-dienes **7a**–**d**,**g**

Compounds **6a**–**d**,**g** were relatively unstable so they were immediately engaged in the Suzuki cross-coupling step with a potassium vinyl trifluororate salt. Suzuki reaction was performed using a procedure developed by Molander[19] to give the desired 1,3-dienes **7a**–**d**,**g** in moderate overall yields (15–44%).

In order to obtain 1,3-dienes bearing an electron-rich group (alkyl or *p*-methoxyphenyl) in position 2, we explored an alternative strategy (Scheme 3). We reasoned that, instead of performing a bromination on **4** and then a Suzuki cross-coupling, one could install the terminal dou-

ble bond by Michael addition of vinylmagnesium bromide onto **4** and that the initial double bond could be re-formed by α-selenylation, oxidation and subsequent elimination of the selenoxide. Application of this strategy to **4e**,**f** and **4h**[20] allowed obtaining of the corresponding 1,1-dicarbonyl ester 1,3-dienes **7e**,**f**,**h** in moderate overall yields (14–22%).



Scheme 3 Synthesis of 1,3-dienes bearing an electron-rich group in position 2 (**7e**,**f**,**h**)

In summary, we have developed practical methods to synthesize various monosubstituted 1,1-dicarbonyl ester 1,3-dienes.[21] The development of new methodologies using these dienes and their application to the synthesis of biologically important targets is currently underway in our laboratory.

Acknowledgment

This work was supported by the Fonds de la Recherche Scientifique-FNRS (F.R.S.-FNRS), the FRIA (fellowship to O.R.) and the FSR (fellowship to T.D.). R.R. is a Chercheur qualifié of the F.R.S.-FNRS.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) General procedures are reported below while characterization of all synthesized compounds (dienes and intermediates) is given in the Supporting Information.
Synthesis of Dimethyl (2-Methylprop-2-en-1-ylidene)malonate (2a): In a round-bottomed flask was added THF (12 mL), under argon. A solution of $TiCl_4$ (6 mmol) in CCl_4 (1.5 mL) was then added, slowly, at 0 °C. After 10 min, methacrolein (3 mmol) and dimethyl malonate (1.5 mmol) were added dropwise. The solution was stirred at 0 °C for 20 min. Pyridine (12 mmol) was then added dropwise and the solution was allowed to warm to r.t. After 16 h of stirring, the reaction mixture was diluted with Et_2O (10 mL) and H_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The organic phases were combined, washed with a sat. $NaHCO_3$ solution (10 mL) and then brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.
Typical Procedure for the Knoevenagel Condensation Reaction (3 → 4): In a one-necked round-bottomed flask were added malonate (93 mmol) and aldehyde **3** (110 mmol) in absolute EtOH (40 mL). AcOH (17 mmol) and piperidine (13 mmol) were then added dropwise. The solution was heated at reflux for 48 h (110 °C). The by-product was then distilled in a Kugelrohr apparatus under reduced pressure to yield the diene in an excellent yield.
Typical Procedure for the Bromination Reaction (4 → 5): In a one-necked round-bottomed flask were added diethyl malonate compound **4** (8 mmol) and bromine (10 mmol) in CCl_4 (8 mL), at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then at r.t. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), then washed with a solution of 1 M NaOH (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the desired compound in a good yield.
Typical Procedure for the Elimination Reaction (5 → 6): In a one-necked round-bottomed flask, under argon atmosphere, was added the dibromo compound **5** (2.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C. DBU (3.5 mmol) was then added slowly and the reaction mixture was stirred at 0 °C for 30 min. It was then diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL). A solution of 1 M HCl (10 mL) was added and the two phases were separated. The organic phase was dried over $MgSO_4$, filtered and concentrated. The compound was relatively unstable and was therefore engaged immediately in the next step without further purification.
Typical Procedure for the Suzuki Reaction (6 → 7): In a one-necked round-bottomed flask, under argon atmosphere, were added the monobromo compound **6** (3.6 mmol), potassium vinyltrifluoro-borate (4.3 mmol) and $PdCl_2$dppf (0.18 mmol) in a solution of EtOH (20 mL) and Et_3N (5.3 mmol) previously degassed. The reaction mixture was heated at 40 °C for 16 h and then concentrated under vacuum. The residue was diluted with EtOAc (40 mL), washed successively with H_2O (20 mL), a solution of sat. NH_4Cl (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography with a mixture of cyclohexane and EtOAc.
Typical Procedure for Michael Addition (4 → 8): CuI (2.8 mmol) was dissolved in THF (20 mL) under inert atmosphere. A 0.583 M solution of vinylmagnesium bromide in THF (10.1 mL, 5.9 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 45 min at this temperature. A solution of compound **4** (2.3 mmol) in THF (20 mL) was then added dropwise at –78 °C. The reaction mixture was stirred overnight (the cooling bath warming slowly to r.t.). The reaction was quenched with a sat. NH_4Cl solution (5 mL) and diluted with H_2O (10 mL) and Et_2O (50 mL). After layers separation, the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and finally concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc–cyclohexane, 10:90) to give the desired product.
Typical Procedure for Double Bond Reformation (8 → 7): Compound **8** (1 mmol) was dissolved in DMF (5 mL) under inert atmosphere. NaH (60% dispersion in mineral oil; 1.2 mmol) was then added at 0 °C. The mixture was stirred for 1 h at r.t. (= solution A).
In another flask PhSeCl (2 mmol) was dissolved in DMF (5 mL). This solution was cooled to –10 °C, and then added, very slowly (over 2 h) to solution A. This mixture was stirred for two more hours at –10 °C and then for 2 h at 0 °C. H_2O_2 (30% solution in H_2O; 15 mmol) was added at 0 °C and the solution was stirred for 30 min at this temperature. The reaction was quenched with a sat. $NaHCO_3$ solution (5 mL), diluted with H_2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5:95 → 10:90, EtOAc–cyclohexane) to give the desired product.

