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Carbon Nucleophiles in the Mitsunobu Reaction. Mono- and Dialkylation of Bis(2,2,2-trifluoroethyl) Malonates

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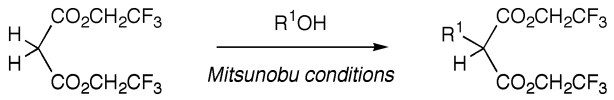
ABSTRACT



Simple dialkyl malonate esters, for example diethyl malonate, exhibit relatively limited scope as carbon nucleophiles in the Mitsunobu dehydrative alkylation reaction. In contrast, bis(2,2,2-trifluoroethyl) malonate readily undergoes dehydrative alkylation with primary alcohols, and using only a slight excess of malonate gives monoalkylated product in good yield. Some secondary alcohols can also be employed, and bis(2,2,2-trifluoroethyl) malonates can be used in a second dehydrative alkylation to give dialkylated products in good to excellent yield.

The Mitsunobu reaction is a versatile method for the coupling of an alcohol (R^1OH) with a pronucleophile (H-Nu) to form the dehydrative alkylation product (R^1-Nu) (Scheme 1).[1] The

Scheme 1

$$R^1\text{—OH} + \text{H—Nu} + Ph_3P + RO_2CN{=}NCO_2R \longrightarrow R^1\text{—Nu} + Ph_3PO + RO_2CNHNHCO_2R$$

reaction typically employs a triaryl- or trialkylphosphine and an azodicarboxylate as stoichiometric reagents to activate the coupling components and has been extensively studied with regard to its mechanism[2] and widely used, particularly with heteroatom pronucleophiles, in organic synthesis.[1,3] The Mitsunobu reaction requires a relatively acidic pronucleophile,[4] and its utility in carbon−carbon bond formation is limited due to the relatively low acidity of most carbon acids. For example, simple malonic esters such as diethyl malonate are not efficient nucleophiles for the Mitsunobu condensation,[5] especially under the original conditions employing diethyl diazodicarboxylate (DEAD) and triphenylphosphine.

The lack of reactivity exhibited by malonates is attributed to their relatively weak acidity; the pK_a of diethyl malonate in water is 13.3.[6] To expand the utility of carbon nucleophiles, two general improvements have been sought: the development of more acidic carbon nucleophiles, and the development of alternative coupling reagents. Considerable progress has been made in the latter approach, and a number of reaction protocols now prove more effective than the original recipe[7,8] and/or are tuned for specialty applications.[9]

Some of the newer procedures are reported to be useful for the alkylation of diethyl malonate,[8,10] but more commonly, more acidic active methylene compounds or related

(1) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127−164.

(2) (a) Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754−1759. (b) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751−1753. (c) Watanabe, T.; Gridnev, I. D.; Imamoto, T. *Chirality* **2000**, *12*, 346−351. (d) Eberson, L.; Persson, O.; Svensson, J. O. *Acta Chem. Scand.* **1998**, *52*, 1293−1300. (e) Shull, B. K.; Sakai, T.; Nichols, J. B.; Koreeda, M. *J. Org. Chem.* **1997**, *62*, 8294−8303.

(3) (a) Simon, C.; Hosztafi, S.; Makleit, S. *J. Heterocycl. Chem.* **1997**, *34*, 349−365. (b) Wisniewski, K.; Koldziejczyk, A. S.; Falkiewicz, B. *J. Pept. Sci.* **1998**, *4*, 1−14.

(4) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172−7174.

(5) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, 1279−1282.

(6) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439−2443.

(7) (a) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518−2521. (b) Zaragoza, F.; Stephensen, H. *Tetrahedron* **2001**, *57*, 5451−5454. (c) Steinreiber, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett.* **2001**, *42*, 6283−6286. (d) Ito, S.; Tsunoda, T. *Pure Appl.*

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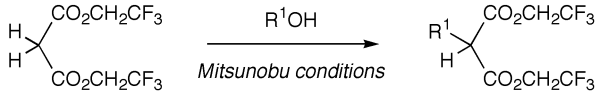
derivatives and synthetic equivalents are employed.[11] For example, Shing reported the *C*-alkylation of Meldrum's acid under Mitsunobu conditions.[12] Its alkylation works using a limited range of alcohols, principally, primary allylic or arylmethyl alcohols, and only dialkylated products are obtained. Attempts to selectively monoalkylate failed. The problem of dialkylation is inherent in such reactions and is seen even in polymer-bound applications, where the reacting partners are constrained.[13]

We were encouraged that, while not suitable for our use, Meldrum's acid derivatives were at least sufficiently reactive to participate in the Mitsunobu reaction. We reasoned that by appropriate choice of the ester substituent another malonate derivative with suitable acidity could be found. We carried out the reaction of diphenyl malonate with allyl alcohol and obtained a mixture of *O*- and *C*-alkylation products, with the former predominating by about 2:1. The problem of regiocontrol in the Mitsunobu reaction of ambident nucleophiles is inherent to such substrates.[4,14]

We next investigated the reaction of bis(2,2,2-trifluoroethyl) malonate (**1**), a compound that has been described in both the open and patent literature for other purposes.[15] Fluorine-containing compounds have been used in Mitsunobu reactions, most frequently as substituents in the alcohol component or in the development of fluorous reaction conditions and fluorous-based separations.[16] The reaction of **1** was examined under three sets of frequently used Mitsunobu conditions (Table 1).

Table 1. The Monoalkylation of Bis(2,2,2-trifluoroethyl) Malonate (**1**) under Three Common Mitsunobu Conditions



1

2a (R^1 = $PhCH_2CH_2CH_2$)
2b (R^1 = $PhCH_2$)

entry	R^1OH	method[a]	product	yield (%)
1	$Ph(CH_2)_3OH$	A	**2a**	40
2	$Ph(CH_2)_3OH$	B	**2a**	84
3	$Ph(CH_2)_3OH$	C	**2a**	82
4	$PhCH_2OH$	A	**2b**	41
5	$PhCH_2OH$	B	**2b**	63[b]

[a] Reaction conditions: A mixture of **1** (1.1 equiv), alcohol (1.0 equiv), phosphine (1.5 equiv), and azo compound (1.5 equiv) in dry toluene at room temperature. Methods: (A) DEAD-Ph_3P; (B) ADDP-Ph_3P; and (C) ADDP-Bu_3P. [b] Bis(2,2,2-trifluoroethyl) dibenzylmalonate was isolated in 27% yield.

Under the original Mitsunobu DEAD-Ph_3P conditions, dehydrative coupling with a simple primary alcohol test substrate, 3-phenyl-1-propanol, gives the desired *C*-alkylated product **2a** in 40% yield (Table 1, entry 1). However, using the 1,1′-(azodicarbonyl)dipiperidine (ADDP)-Ph_3P or ADDP-Bu_3P reagents,[8] the monoalkylated product **2a** was obtained in greater than 80% yield (Table 1, entries 2 and 3, respectively). Benzyl alcohol behaves similarly, although the combination of a more reactive alcohol and the more reactive ADDP reagent gives a significant amount of the dialkylated product (27%) in addition to the major monoalkylated product **2b** (63%).

Having identified bis(2,2,2-trifluoroethyl) malonate (**1**) as a malonate derivative suitable for use in the ADDP-Ph_3P promoted Mitsunobu reaction, and finding that it reacts via *C*-alkylation and can be selectively monoalkylated, other aspects probing the scope of reaction were investigated. The starting materials, products, and data obtained are summarized in Table 2. With a limiting amount of allyl alcohol, the reaction proceeds much like that of benzyl alcohol; the monoalkylated product **2c** is obtained in 60% yield (entry 1). Using an excess of the alcohol and coupling components, malonate **1** can be efficiently dialkylated. For example, in the presence of excess allyl alcohol, the dialkylated malonate **3a** was formed in 92% yield (entry 2). Similarly, starting with the monoalkylated malonate **2a**, dehydrative alkylation

Chem. **1999**, *71*, 1053−1057. (e) Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999**, *40*, 4497−4500. (f) Tsunoda, T.; Kawamura, Y.; Uemoto, K.; Ito, S. *Heterocycles* **1998**, *47*, 177−179. (g) Kawamura, Y.; Sato, Y.; Horie, T.; Tsukayama, M. *Tetrahedron Lett.* **1997**, *38*, 7893−7896. (h) Tsunoda, T.; Ito, S. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 631−641. (i) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett.* **1994**, 539−542. (j) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081−5082.

(8) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639−1642.

(9) For example: (a) Ryoo, S.-J.; Kim, J.; Kim, J.-S.; Lee, Y.-S. *J. Comb. Chem.* **2002**, *4*, 187−190. (b) Li, Z.; Zhou, Z.; Wang, L.; Zhou, Q.; Tang, C. *Tetrahedron: Asymmetry* **2002**, *13*, 145−148. (c) Chandrasekhar, S.; Kulkarni, G. *Tetrahedron: Asymmetry* **2002**, *13*, 615−619. (d) Charette, A. B.; Janes, M. K.; Boezio, A. A. *J. Org. Chem.* **2001**, *66*, 2178−2180. (e) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *J. Org. Chem.* **2001**, *66*, 8273−8276. (f) Viirre, R. D.; Hudson, R. H. E. *Org. Lett.* **2001**, *3*, 3931−3934. (g) Winum, J. Y.; Barragan, V.; Montero, J. L. *Tetrahedron Lett.* **2001**, *42*, 601−603.

(10) Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2531−2534.

(11) (a) Macor, J. E.; Wehner, J. M. *Tetrahedron Lett.* **1991**, *32*, 7195−7198. (b) Yu, J. R.; Cho, H. S.; Falck, J. R. *J. Org. Chem.* **1993**, *58*, 5892−5894. (c) Lai, J. Y.; Yu, J. R.; Hawkins, R. D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691−5694. (d) Yu, J. R.; Lai, J. Y.; Falck, J. R. *Synlett* **1995**, 1127−1128. (e) Tsunoda, T.; Nagino, C.; Oguri, M.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2459−2462. (f) Cravotto, G.; Glovenzana, G. B.; Sisti, M.; Palmisano, G. *Tetrahedron* **1996**, *52*, 13007−13016. (g) Tsunoda, T.; Uemoto, K.; Ohtani, T.; Kaku, H.; Ito, S. *Tetrahedron Lett.* **1999**, *40*, 7359−7362. (h) Uemoto, K.; Kawahito, A.; Matsushita, N.; Sakamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* **2001**, *42*, 905−907.

(12) Shing, T. K. M.; Li, L. H.; Narkunan, K. *J. Org. Chem.* **1997**, *62*, 1617−1622.

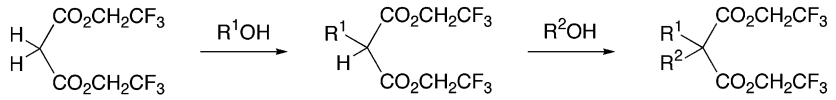
(13) Chaturvedi, S.; Otteson, K.; Bergot, J. *Tetrahedron Lett.* **1999**, *40*, 8205−8209.

(14) (a) Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819−2822. (b) Wang, J.; Gutsche, C. D. *Struct. Chem.* **2001**, *12*, 267−274. (c) Attolini, M.; Boxus, T.; Biltresse, S.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2002**, *43*, 1187−1188.

(15) (a) Mozhaev, V. V.; Budde, C. L.; Rich, J. O.; Usyatinsky, A. Y.; Michels, P. C.; Khmelnitsky, Y. L.; Clark, D. S.; Dordick, J. S. *Tetrahedron* **1998**, *54*, 3971−3982. (b) Lei, Y. X.; Cerioni, G.; Rappoport, Z. *J. Org. Chem.* **2001**, *66*, 8379−8394. (c) Romanovskiy, V. N.; Smirnov, I. V.; Babain, V. A.; Todd, T. A.; Herbst, R. S.; Law, J. D.; Brewer, K. N. *Solvent Extr. Ion Exch.* **2001**, *19*, 1−21.

(16) (a) Fokina, N. A.; Kornilov, A. M.; Kukhar, V. P. *J. Fluorine Chem.* **2001**, *111*, 69−76. (b) Bes, L.; Rousseau, A.; Boutevin, B.; Mercier, R.; Kerboua, R. *Macromol. Chem. Phys.* **2001**, *202*, 2954−2961. (c) Hein, M.; Miethchen, R. *Eur. J. Org. Chem.* **1999**, 2429−2432. (d) Rabai, J.; Szabo, D.; Borbas, E. K.; Kovesi, I.; Kovesdi, I.; Csampai, A.; Gomory, A.; Pashinnik, V. E.; Shermolovich, Y. G. *J. Fluorine Chem.* **2002**, *114*, 199−207. (e) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855−3864. (f) Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807−2810.

Table 2. Dehydrative Mono- and Dialkylations of Bis(2,2,2-trifluoroethyl) Malonates **1** and **2**[a]



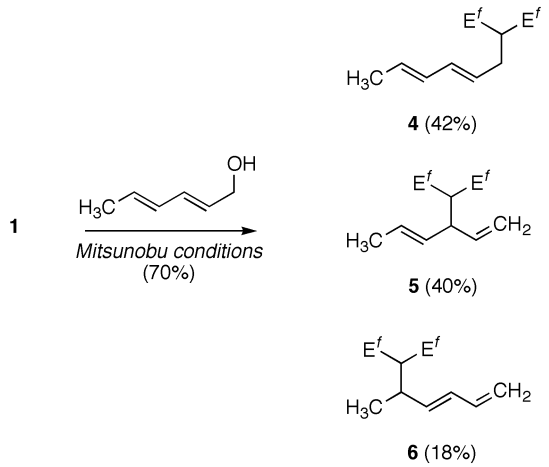
1 **2** **3**

entry	NuH	alcohol	prod	R^1	R^2	yield (%)
1[b]	**1**	$H_2C{=}CHCH_2OH$	**2c**	$H_2C{=}CHCH_2$	H	60
2[c]	**1**	$H_2C{=}CHCH_2OH$	**3a**	$H_2C{=}CHCH_2$	$H_2C{=}CHCH_2$	92
3	**2a**	$H_2C{=}CHCH_2OH$	**3b**	$PhCH_2CH_2CH_2$	$H_2C{=}CHCH_2$	96
4[d]	**1**	(*E*)-$PhCH{=}CHCH_2OH$	**2d**	(*E*)-$PhCH{=}CHCH_2$	H	76
5	**2l**	(*E*)-(*n*-$Bu)_3SnCH{=}CHCH_2OH$	**3c**	$H_2C{=}CHCH{=}CH(CH_2)_2$	(*n*-$Bu)_3SnCH{=}CHCH_2$	86
6	**1**	$H_3CCH{=}CHCH(CH_3)OH$[e]	**2e**[e]	$H_3CCH{=}CHC(CH_3)H$	H	54
7	**1**	$(HC{\equiv}C)CH(CH_3)OH$	**2f**	$(HC{\equiv}C)CH(CH_3)$	H	23
8	**1**	$H_2C{=}CHCH_2CH(CH_3)OH$	**2 g**	$H_2C{=}CHCH_2C(CH_3)H$	H	trace
9[f]	**1**	(*E*) $H_3C(CH_2)_2CH{=}CHCH_2OH$	**2h**	$H_3C(CH_2)_2CH{=}CHCH_2$	H	35
			2i	$H_3C(CH_2)_2CHCH{=}CH_2$	H	15
10[d]	**1**	$(CH_2{=}CH)_2C(H)OH$	**2j**[e]	$H_2C{=}CHCH{=}CHCH_2$	H	52
11[d]	**1**	H_3COH	**2k**	H_3C	H	58
12	**2a**	$H_2C{=}CH(CH_2)_3OH$	**3d**	$PhCH_2CH_2CH_2$	$H_2C{=}CH(CH_2)_3$	89
13	**1**	$H_2C{=}CHCH{=}CH(CH_2)_2OH$	**2l**	$H_2C{=}CHCH{=}CH(CH_2)_2$	H	56
14[c]	**1**	$H_2C{=}CHCH{=}CH(CH_2)_2OH$	**3e**	$H_2C{=}CHCH{=}CH(CH_2)_2$	$H_2C{=}CHCH{=}CH(CH_2)_2$	75
15	**2l**	$H_2C{=}CHCH{=}CH(CH_2)_3OH$	**3f**	$H_2C{=}CHCH{=}CH(CH_2)_2$	$H_2C{=}CHCH{=}CH(CH_2)_3$	75
16[c]	**1**	$H_2C{=}CHCH{=}CH(CH_2)_3OH$	**3g**	$H_2C{=}CHCH{=}CH(CH_2)_3$	$H_2C{=}CHCH{=}CH(CH_2)_3$	63

[a] Reaction conditions (unless otherwise noted): A mixture of alcohol (1 equiv), **1** or **2** (1.1 equiv), Ph_3P (1.5 equiv), and ADDP (1.5 equiv) in dry toluene at room temperature. The course of the reaction is followed by TLC. [b] A small amount of dialkylated product **3a** was also obtained. [c] **1** (1.0 equiv), alcohol (2.5 equiv), Ph_3P (3.5 equiv), and ADDP (3.75 equiv) in dry toluene at room temperature. [d] This reaction was run at 0 °C; when run at room temperature, the yield was lower. [e] Predominantly *E*. [f] An inseparable 2.4:1 mixture of **2h**:**2i** is obtained in 50% yield.

with allyl alcohol affords the dialkylated malonate ester **3b** in high yield (96%, entry 3).

Scheme 2



A secondary allylic alcohol, 3-penten-2-ol, gives monoalkylated product (i.e., **2e**) in yield comparable to that achieved with allyl alcohol (54%, entry 6). In contrast, a secondary propargylic alcohol affords a modest yield of product (23%, entry 7), and a simple unactivated secondary alcohol, 4-penten-2-ol, gives only a trace of alkylated product **2g** under these reaction conditions (entry 8).

Returning to the discussion of primary allylic alcohols, higher homologues can substitute in an S_N2 or S_N2' fashion, and the extent of regioselectivity depends on the nature of the alkene substituent. For example, cinnamyl alcohol (entry 4) and a vinyl tin derivative (entry 5) react with high regioselectivity for the S_N2 pathway, while *trans*-2-hexen-1-ol affords a 2.4:1 mixture that favors the S_N2 mode (entry 9). In contrast, divinyl alcohol reacts almost exclusively via the S_N2' mode to afford the conjugated diene, **2j** (entry 10). 2,4-Hexadien-1-ol (Scheme 2) reacts with **1** in good yield (70% of monoalkylated product), but affords an unfavorable mixture of regioisomeric products **4**, **5**, and **6**. Entries 11−16 in Table 2 further illustrate the use of primary alcohols as Mitsunobu electrophiles for mono- or double-dehydrative alkylation.

In summary, the alkylations of bis(2,2,2-trifluoroethyl) malonates under typical Mitsunobu conditions provide mono- or dialkylated products in good to excellent yield and establish these malonates as convenient, practical carbon nucleophiles for the Mitsunobu dehydrative alkylation method.

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Supporting Information Available: Spectral data for compounds **1**−**4** as well as representative procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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