## Addition of Polyfunctional and Pure (*E* or *Z*) Alkenylcopper and Arylcopper Compounds to Alkylidenemalonates

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Polyfunctional and stereochemically pure (*E*) or (*Z*) alkenylcopper reagents have been generated by carbocupration of terminal alkynes or by an iodine–lithium exchange reaction and have been found to add to various diethyl alkylidenemalonates, affording  $\gamma$ , $\delta$ -unsaturated esters in excellent yields.

Aryl- and alkenyl-copper reagents are considerably less reactive than alkylcopper derivatives and undergo 1,4-additions less efficiently than their alkyl-counterparts, especially in the case of unreactive Michael acceptors such as unsaturated esters.<sup>1.2</sup> In spite of the fact that alkylidenemalonic esters are good synthetic equivalents of enoates and are much more reactive, they have been used little with vinyl or aryl copper reagents.<sup>3</sup>

We report herein reaction conditions allowing the generation of stereochemically pure simple or functionalized alkenylcopper compounds and their successful addition to diethyl alkylidenemalonates. Two methods were used for the preparation of the copper organometallics: (*i*) the well-known carbocupration of terminal alkynes by Grignard-derived copper reagents in diethyl ether,<sup>4</sup> and (*ii*) an iodine–lithium exchange reaction, followed by a transmetallation.<sup>5</sup>



Scheme 1 Reagents and conditions: i, CuI, diethyl ether, -35 °C, 0.5 h; ii, R<sup>2</sup>C=CH, -15 to -10 °C, 1.5 h



Scheme 2 Reagents and conditions: i, diethyl ether-THF, -10 to 25 °C, 3 h

**Table 1** Unsaturated malonic esters 4 prepared by the addition of pureZ or E alkenylcopper compounds 2 to alkylidenemalonates 3

Product 4	$\mathbf{R}^1$	<b>R</b> <sup>2</sup>	<b>R</b> <sup>3</sup>	<b>R</b> <sup>4</sup>	Yield $(\%)^a$
(Z)-a (E)-a b c d d e f f g h	Pent Et Et Bu Et Bu Bu Bu	Et Pent Pent Pent Pent Dec Pent Dec	Me Pr Pr <sup>i</sup> Ph Pr <sup>i</sup> Me Me	H H H H H H Me Me	$71 \\ 80 \\ 58 \\ 71 \\ 68^{b} \\ 90^{b} \\ 60^{b} \\ 60^{b} \\ 58^{b}$
i	Et	Pent	Н	Н	67 <sup>c</sup>

<sup>*a*</sup> Isolated yields of analytically pure products, all reactions were performed at a 30 mmol scale. <sup>*b*</sup> Reaction performed in ether without the addition of THF. <sup>*c*</sup> Reaction performed in the presence of Me<sub>3</sub>SiBr (1.2 equiv.).

Thus, the slow addition of an alkylmagnesium bromide (R<sup>1</sup>MgX) to a suspension of CuI in diethyl ether at -35 °C provides a yellow precipitate of R<sup>1</sup>Cu·MgX<sub>2</sub> **1** which reacts readily with a terminal alkyne (1.0 equiv., -35 °C, then -15 to -10 °C, 1.5 h) to give a dark-green solution of alkenyl-copper **2** (Scheme 1). The addition of a diethyl alkylidenemalonate **3** (1.0 equiv.) and tetrahydrofuran (THF) (2 ml per mmol of the alkyne) at -10 °C and warming up of the reaction mixture to room temperature gives a grey suspension which after the usual work-up furnishes the desired 1,4-adduct **4** with complete retention of the double bond geometry<sup>+</sup> in excellent yields (Scheme 2 and Table 1). Attempts to improve the yields by adding triethylphosphite, *N*-methylpyrrolidone or Me<sub>3</sub>SiCl<sup>6</sup> did not succeed.

The use of an excess (20 mol%) of the alkenylcopper **2** did not lead to significantly higher yields. Interestingly, the addition of **2** to diethyl methylidenemalonate ( $R^3 = R^4 = H$ )<sup>7</sup> proceeds only in 52% yield under the standard reaction conditions, however, the addition of Me<sub>3</sub>SiBr (1.2 equiv.) leads to substantial improvement<sup>8</sup> and affords **4i** in 67% isolated yield. In the case of  $\beta$ , $\beta$ -disubstituted alkylidenemalonates, the use of diethyl ether alone as solvent provides the best yields. This relatively nonpolar solvent reduces the enolization of the alkylidenemalonate.

Vinylic copper compounds prepared by the addition of alkylcoppers to terminal alkynes in diethyl ether are especially unreactive toward Michael-acceptors. They do not react with  $\alpha$ , $\beta$ -unsaturated ketones or esters, even in the presence of BF<sub>3</sub>·Et<sub>2</sub>O or after addition of THF as cosolvent.<sup>4d</sup> It is



Scheme 3 Reagents and conditions: i, BuLi (1.05 equiv.), THF: diethyl ether: pentane (2:1:1), -100 °C; ii, CuI-2LiI (1.0 equiv.), THF: Me<sub>2</sub>S (1:1), -100 to -30 °C



**Table 2** Polyfunctional malonic esters **8a–j** obtained by the reaction of polyfunctional pure *E* alkenyl- and aryl-copper compounds **7** with alkylidenemalonates **3** ( $\mathbb{R}^3 = \text{c-Hex or Ph}$ )

Organocopper reagent 7	Alkylidene- malonate R <sup>3</sup>	Product <b>8</b> R <sup>3</sup> (R)CH–CH(CO <sub>2</sub> Et) <sub>2</sub>	Yield (%) <sup>a</sup>
$(E)-HexC(H)=C(H)Cu$ $(E)-HexC(H)=C(H)Cu$ $(F)Cl(CH_{2})+C(H)=$	Ph c-Hex	<b>a</b> : R = ( <i>E</i> )-HexCH=CH- <b>b</b> : R = ( <i>E</i> )-HexCH=CH-	95 90
C(H)Cu	Ph	c: $R = (E)$ -Cl(CH <sub>2</sub> ) <sub>3</sub> - CH=CH-	80
(E)-Cl(CH <sub>2</sub> ) <sub>3</sub> C(H)= C(H)Cu	c-Hex	<b>d</b> : $\mathbf{R} = (E)$ -Cl(CH <sub>2</sub> ) <sub>3</sub> - CH=CH-	71
(E)-NC(CH <sub>2</sub> ) <sub>3</sub> C(H)= C(H)Cu	Ph	e: $\mathbf{R} = (E)\mathbf{NC}(\mathbf{CH}_2)_3$ - CH=CH-	82
(E)-Bu <sup>t</sup> CO <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> - C(H)=C(H)Cu	Ph	f: $\mathbf{R} = (E)$ -Bu <sup>t</sup> CO <sub>2</sub> - (CH <sub>2</sub> ) <sub>2</sub> CH=CH-	76
p-NCC <sub>6</sub> H <sub>4</sub> Cu p-NCC <sub>6</sub> H <sub>4</sub> Cu p-Bu <sup>1</sup> O <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> Cu p-Bu <sup>1</sup> O <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> Cu	Ph c-Hex Ph c-Hex	g: $R = p-NCC_6H_4$ - h: $R = p-NCC_6H_4$ - i: $R = p-Bu^4O_2CC_6H_4$ - j: $R = p-Bu^4O_2CC_6H_4$ -	90 92 85 79

<sup>*a*</sup> Isolated yields of analytically pure products; all reactions were performed at a 4–6 mmol scale.

necessary to carry out the reaction in a mixture  $Et_2O:Me_2S$  ( $\approx 1:1$ ) as solvent to perform the 1,4-addition to reactive enones (*e.g.* cyclohexenone) successfully.<sup>9</sup> Moreover, under these conditions, the conjugate addition to enoates only occurs after conversion of the vinyl copper **2** in the more reactive vinyl alkynyl cuprate [R<sup>1</sup>R<sup>2</sup>C=CH(BuC=C)]CuLi.<sup>9</sup> This is very surprising since vinyl copper reagents prepared by lithium–copper or magnesium–copper exchange react with enones to give the conjugate addition product in good yields.<sup>10</sup> The results described in Table 1 are the first successful examples of conjugate addition of vinyl coppers prepared by carbocupration in diethyl ether occurring without any additive.

Polyfunctional alkeny- or aryl-copper reagents can also be added successfully to alkylidenemalonates. These were prepared by treating the corresponding functionalized aromatic or vinylic iodides **5** with BuLi (1.05 equiv.) at -100 °C in the Trapp mixture<sup>10.11</sup> (2:1:1, THF:diethyl ether:pentane). After 3 min at this temperature, the intermediate lithium compound **6** was formed and a solution of CuI·2LiI (1.0 equiv., -100 to -80 °C in 1:1 THF:Me<sub>2</sub>S) was added resulting in the formation of a dark-red solution of the corresponding copper reagent **7** (Scheme 3). In the case of the aromatic copper reagents prepared from the corresponding aromatic bromides, CuCN·LiCl<sup>12</sup> was used. It should be noted that the preparation of the functionalized vinyl copper

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<sup>&</sup>lt;sup>†</sup> Comparison between the <sup>1</sup>H and <sup>13</sup>C spectra of (*E*) and (*Z*) **4a** (Table 1) show the absence of the other stereoisomer in each product. For the stereochemistry of the carbocupration see ref. 4(b).

scribed by some of us for the first time.<sup>13</sup> Remarkably, this procedure permits the preparation of polyfunctional (*E*)-alkenylcopper compounds **7** which add readily to alkylidenemalonates **3** (0.67–0.8 equiv., -30 to 25 °C, 1–5 h) to furnish the desired Michael-adducts **8a–j** in good yields (71–95%; Scheme 4 and Table 2). The adducts can be decarboxylated to  $\gamma$ , $\delta$ -unsaturated esters using Krapcho's procedure<sup>14</sup> and the diethyl alkylmalonate **4a** was converted to pure (*E*)-ethyl 5-ethyl-3-methyldec-4-enoate in 76% unoptimized yield (50 mmol scale reaction).

In conclusion, we have prepared a variety of pure (E) or (Z)- $\gamma$ , $\delta$ -unsaturated malonates by the stereospecific addition of alkenyl and aryl copper reagents to alkylidene malonates. Remarkably, the reaction tolerates the presence of an ester, halide or nitrile function in the organometallic moiety. After decarboxylation of the conjugated adduct according to Krapcho procedure,<sup>14</sup> this method allows to prepare various pure (E) or  $(Z) \gamma$ , $\delta$ -unsaturated esters which are very difficult to obtain from the corresponding enoates. Further applications are underway.

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## References

- Y. Yamamoto and K. Maruyama, J. Am. Chem. Soc., 1977, 99, 8068; Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, J. Org. Chem., 1982, 47, 119; W. Oppolzer and H. J. Loher, Tetrahedron Lett., 1983, 24, 4971; B. H. Lipshutz, Tetrahedron Lett., 1983, 24, 127.
- 2 For excellent reviews see: Y. Yamamoto, Angew. Chem., Int. Ed. Engl., 1986, 25, 947; B. H. Lipshutz, R. S. Wilhelm and J. A. Kozlowski, Tetrahedron, 1984, 40, 5005; J. A. Kozlowski, in Comprehensive Organic Synthesis ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. IV, p. 169.

## J. CHEM. SOC., CHEM. COMMUN., 1992

- 3 Copper-catalysed addition of a vinyl grignard reagent to alkylidene malonic esters has been reported in moderate yield: T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 1961, 1423.
- 4 (a) J. F. Normant and M. Bourgain, *Tetrahedron Lett.*, 1971, 2583;
  (b) J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit and J. Villieras, *Bull. Soc. Chim. Fr.*, 1974, 1656; (c) J. F. Normant and A. Alexakis, *Synthesis*, 1981, 841; (d) G. Cahiez, Thesis, University Pierre and Marie Curie, Paris, France, 1973.
- 5 G. Cahiez, D. Bernard and J. F. Normant, Synthesis, 1976, 245; D. Seebach and H. Neumann, Chem. Ber., 1974, 107, 847; H. Neumann and D. Seebach, Tetrahedron Lett., 1976, 4839.
- 6 C. Chuit, J. P. Foulon and J. F. Normant, *Tetrahedron*, 1980, 36, 2305; C. Chuit, J. P. Foulon and J. F. Normant, *Tetrahedron*, 1981, 37, 1385; E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 1985, 26, 6019; Y. Horiguchi, S. Matsuzawa, E. Nakamura and I. Kuwajima, *Tetrahedron Lett.*, 1986, 27, 4025; A. Alekakis, J. Berlan and Y. Besace, *Tetrahedron Lett.*, 1986, 27, 1047.
- 7 Preparation of diethyl methylidenemalonate: G. B. Bachman and H. A. Tanner, *J. Org. Chem.*, 1939, **4**, 493.
- 8 M. Bergdahl, E.-L. Lindstedt, M. Nilsson and T. Olsson, *Tetrahedron*, 1989, 45, 535; M. Bergdahl, E.-L. Lindstedt and T. Olsson, *J. Organomet. Chem.*, 1989, 365, C11–C14; M. Bergdahl, E.-L. Lindstedt, M. Nilsson and T. Olsson, *Tetrahedron*, 1989, 45, 535.
- 9 A. Marfat, P. R. McGuirk, R. Kramer and P. Helquist, J. Am. Chem. Soc., 1977, 99, 255.
- R. L. Funk and K. P. C. Vollhardt, J. Am. Chem. Soc., 1980, 102, 5253; J. Leonard and G. Ryan, *Tetrahedron Lett.*, 1987, 28, 2525.
   For an example of 1,6 addition to a dienoate: E. J. Corey and R. H. Chen, *Tetrahedron Lett.*, 1973, 1611.
- 11 G. Köbrich, Angew. Chem., Int. Ed. Engl., 1967, 6, 41.
- 12 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, J. Org. Chem., 1988, 53, 2390; P. Knochel, M. J. Rozema, C. E. Tucker, C. Retherford, M. Furlong and S. AchyuthaRao, Pure Appl. Chem., 1992, 64, 361.
- 13 We reported recently the preparation of polyfunctional alkenyl and aromatic zinc and copper compounds: C. E. Tucker, T. N. Majid and P. Knochel, J. Am. Chem. Soc., 1992, **114**, 3983.
- A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 1973, 12, 957;
   A. P. Krapcho, *Synthesis*, 1982, 805 and 893.