Synthesis of Highly Substituted Symmetrical 1,3-Dienes via Tandem Carbocupration and Organocuprate Oxidation

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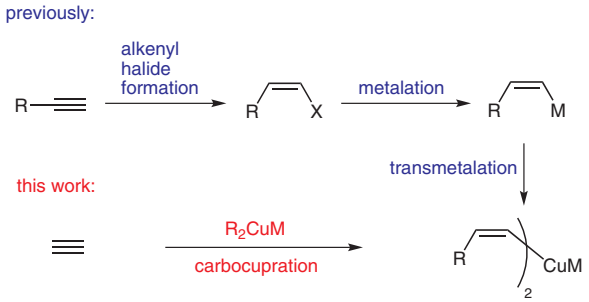
Abstract: A 'one-pot' tandem carbocupration/organocuprate oxidation allows the formation of highly substituted symmetrical 1,3-dienes from alkynyl esters and alkyl organolithium or Grignard reagents with three C–C bonds being formed in one step.

Key words: cuprates, oxidation, carbocupration, 1,3-diene, tandem reaction

The substituted 2,3-bis(alkylidene)succinate motif (**1**) is a versatile building block in organic chemistry, able to undergo a range of reactions including Diels–Alder and Michael additions.[1] It is however difficult to access rapidly, especially in a geometrically pure form with 1,4-substitution.[2]

During the course of our work on organocuprate oxidation[3,4] we demonstrated that aryl and alkenyl organocuprates could be generated from the corresponding halides and oxidatively coupled under the influence of dinitroarene oxidant **5**. As in our work on directed lithiation and oxidation[3b] we reasoned that the use of organohalides could be avoided if another copper-mediated process were used to form the alkenyl cuprate for oxidation: a carbocupration reaction (Scheme 1). This in conjunction with oxidation of the resulting organocuprate would allow molecular complexity to be rapidly built up in a 'one-pot' tandem reaction that would allow access to the desired 2,3-bis(alkylidene)succinate motif.



Scheme 1 Comparison of methods of formation of alkenyl cuprate species (X = I, Br, M = Li, Mg, Zn etc.)

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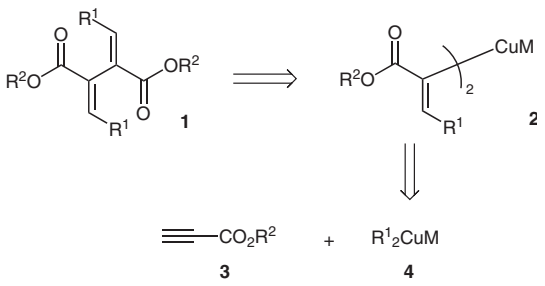
Retrosynthetically it can be envisaged that 1,3-diene **1** can be formed as a result of oxidative homo-coupling of alkenyl cuprate **2** which is in turn formed by the carbocupration of alkynyl ester **3** by organocuprate **4** (Scheme 2). If isomerisation of the alkenyl cuprate is minimised then geometrically pure 1,3-dienes will result. This tandem reaction would allow the formation of three C–C bonds in one step and the desired 1,4-substituted motif to be efficiently built up from simple starting materials, unlike other routes to this class of compound which require the synthesis and isolation of dimethyl bromomethylfumarate.[2b–2d] Isolated reports of tandem carbocupration/oxidation of alkynyl esters in the literature[5,6] highlighted that this was a viable approach to the desired 1,3-diene system and that a study to find more general conditions could prove worthwhile. The disconnection outlined in Scheme 2 is conceptually similar to that of the oxidation of lithium enolates to form 1,4-dicarbonyl compounds[7] but at a different oxidation level. This latter class of reaction has been exploited recently by Baran and co-workers in the total synthesis of several complex natural products.[8]



Scheme 2 Retrosynthetic route to the 1,4-substituted 2,3-bis(alkylidene)succinate motif (M = Li or MgCl)

The geometrical purity of **1** is of vital importance. This requires complete selectivity in the carbocupration and coupling steps. An analysis of the literature suggested that these aspects can be managed by careful choice of reaction conditions.

The carbocupration of an alkynyl ester with a Gilman reagent was first carried out by Corey,[5] closely followed by others.[9] It was found that the ratio of *syn* to *anti* addition products across the alkyne was both solvent and temperature dependent, with ethereal solvents and low temperatures giving the best selectivity. The mechanism of addition was later elucidated by Ullenius and co-

workers[10] via ^{13}C NMR studies, where these workers discovered that the production of the *anti* addition product was as a result of isomerisation of the alkenyl cuprate through an allenolate-type structure. This isomerisation did not take place in THF or if lithium salts were excluded from the cuprate in Et_2O.

Previous studies[11] on the oxidation of alkenyl cuprates produced via carbocupration of substituted acetylenes showed that the homocoupling of the ligands on copper was completely stereoselective, retaining the geometry of the intermediate cuprate.

This information was used to guide the initial optimisation studies which focused upon the formation of **8a**,**b** via the carbocupration of alkynyl esters **7a**,**b** with the organocuprates **6a–c**. We initially examined the conditions of Marino, which utilised a heterocuprate reagent to perform the carbocupration and bromine as the oxidant.[6] This however gave a complex reaction mixture (Table 1, entry 1). We therefore employed a homocuprate in the carbocupration step and also our previously developed dinitroarene oxidant **5** (Figure 1),[3a] which had been successful in oxidising aryl organocuprates and allowed for easy work-up of reaction mixtures.[12] THF was used as solvent and the low reaction temperature was retained as these were thought to be the most favourable conditions for the formation of the desired product (see above). Since different types of oxidant can cause reactions other than homocoupling[11b] of the intermediate cuprate it was pleasing to find that oxidant **5** gave the desired 1,3-diene product (Table 1, entry 2). In addition, both ligands were transferred from the alkyl organocuprate to the alkyne which is not always the case in carbocupration reactions.[13] This is advantageous as it is less wasteful if more complex cuprates resulting from advanced reaction intermediates are used. In these studies minor amounts (ca. 10%) of product resulting from *anti* addition in the carbocupration step were observed; these could be removed in purification by flash column chromatography.

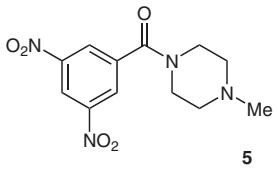


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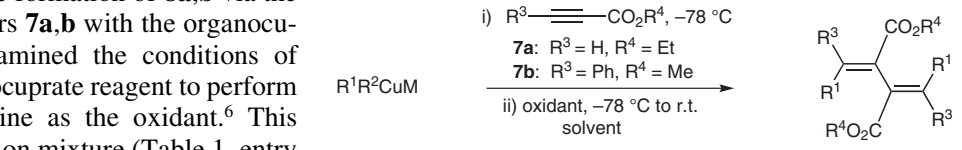
Figure 1 The structure of dinitroarene oxidant **5**

It was also observed that the metal counterion present from the organometallic reagent used to form the initial cuprate **6** affected the outcome of the reaction, with use of a magnesiocuprate giving the best results for the reaction of ethyl propiolate (Table 1, entry 3). However, for the internal alkyne methyl phenylpropiolate, it was the lithiocuprate (Table 1, entry 4) that gave the best results as reactions with the magnesiocuprate did not go to completion and oxidation appeared less facile (Table 1, entry 5). The reason for this selectivity is not immediately clear, but it is possible that the more Lewis acidic magnesium attenuates the basicity of the initial alkyl organocuprate thus avoiding a competing deprotonation of the acetylinic proton in ethyl propiolate. This competing reaction (verses carbocupration) is not an available pathway in the case of internal alkynes. The lack of solution structure studies on magnesiocuprates in the literature makes it difficult to ascertain what effect changing the counterion has on reactivity here. However, it has been noted that changing the cations present in organocuprate clusters alters the reactivity of the complex,[14] which could go some way to explaining this difference in reactivity.

Table 1 Optimisation of Reaction Conditions



6a: R^1 = *n*-Bu, R^2 = *n*-hexynyl
M = Li
6b: $R^1 = R^2$ = *n*-Bu
M = Li
6c: $R^1 = R^2$ = *n*-Bu
M = MgCl

8a,**b**

Entry	Cuprate	Alkynyl ester	Oxidant	Solvent	Yield **8** (%)
1	**6a**	**7a**	Br_2	Et_2O	0
2	**6b**	**7a**	**5**	THF	55[a]
3	**6c**	**7a**	**5**	THF	85
4	**6b**	**7b**	**5**	THF	47
5	**6c**	**7b**	**5**	THF	10

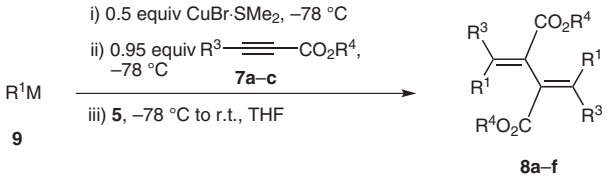
[a] Protonated carbocupration adduct was also isolated in 23% yield.

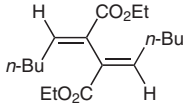
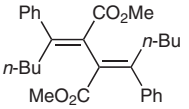
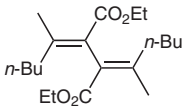
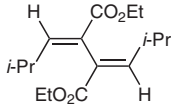
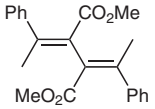
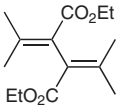
With optimised conditions for the 'one-pot' process in hand, reactions with a range of substitution patterns on both the alkyne and the organocuprate were examined in order to explore the scope of the methodology (Table 2). A slight excess of organocuprate was used in order to push the reaction to completion, as unreacted alkynyl ester had been observed in some of the initial reactions. The appropriate alkyl organometallic reagent was selected according to the substitution pattern of the alkyne in order to maximise yields.

The tandem carbocupration/oxidation reaction proceeded in 22–85% yield, allowing the formation of three C–C bonds in one pot. Use of an excess of alkyl cuprate had the desired effect of increasing the yield in the case of substrate **8b** (Table 2, entry 2). Since these molecules are tetra- and hexa-substituted 1,3-dienes they are necessarily very sterically hindered, and so the fact that they can be formed even with use of the less reactive Me_2CuLi shows the utility of this strategy. It is postulated that the 180° C–Cu–C bond angle and long (1.9 Å) C–Cu bond length[15] enable the formation of these systems as steric clashing between the ligands on copper is minimised during the

course of the reaction. Again, the dienes were formed with high geometrical selectivity and with *syn* addition products predominating; the minor amount of undesired isomer being removed by column chromatography.

Table 2 Synthesis of Symmetrical 1,3-Dienes



Entry	Organometallic **9**	Alkynyl ester	Product	Yield (%)
1	*n*-BuMgCl	**7a**	 **8**[a]	85
2	*n*-BuLi	**7b**	 **8b**	53
3	*n*-BuLi	**7c**	 **8c**	64
4	*i*-PrMgCl	**7a**	 **8d**	22[a]
5	MeLi	**7b**	 **8e**	47
6	MeLi	**7c**	 **8f**	38

[a] Competing Cu acetylide formation observed leading to lower yields.

In conclusion, we have developed a 'one-pot' tandem carbocupration/oxidation of alkynyl esters to allow rapid access to highly substituted symmetrical 1,3-dienes of the 2,3-bis(alkylidene)succinate class.[16] The reaction allows three C–C bonds to be formed in one step, with good *syn* selectivity in carbocupration, and a range of substitution patterns is also tolerated. As molecular complexity can be quickly built up from simple starting materials to yield a versatile synthetic intermediate we envisage that this methodology will prove useful in a wide synthetic context with applications in both target- and diversity-oriented synthesis.[17]

Acknowledgment

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(16) **General Procedure for Tandem Carbocupration/Oxidation Reaction**: A solution of the requisite organometallic reagent (2.10 mmol) was added to a suspension of $CuBr·SMe_2$ (216 mg, 1.05 mmol) in THF

(4 mL) at –78 °C and stirred for 30 min. Alkyne (2.00 mmol) was added dropwise and the reaction was stirred for 3 h at –78 °C. A solution of oxidant **5** (589 mg, 2.00 mmol) in THF (4 mL) was added, the reaction was allowed to stir at –78 °C for 30 min and then allowed to warm to r.t. over 1 h. The resulting solution was filtered through a plug of silica, eluting with either PE–Et_2O (1:1) or *i*-hexane–Et_2O (1:1) and the solvent was removed in vacuo. The residue was purified by flash column chromatography.

(2*E*,3*E*)-Diethyl 2,3-dipentylidenesuccinate (8a): colourless oil; R_f 0.25 (PE–EtOAc, 10:1). IR (Neat): 2957, 2932, 2871, 1712 (C=O), 1631 (C=C), 1464, 1363, 1231, 1206 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.01 (t, 2 H, *J* = 7.6 Hz), 4.16 (q, 4 H, *J* = 7.1 Hz), 2.02 (app q, 4 H, *J* = 7.2 Hz), 1.36–1.46 (m, 4 H), 1.26–1.36 (m, 4 H), 1.24 (t, 6 H, *J* = 7.1 Hz), 0.90 (t, 6 H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5 (C), 146.3 (CH), 127.6 (C), 60.5 (CH_2), 30.3 (CH_2), 29.3 (CH_2), 22.4 (CH_2), 14.2 (Me), 13.8 (Me). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{31}O_4$: 311.2217; found: 311.2217.

(2*Z*,3*Z*)-Dimethyl 2,3-bis(1-phenylpentylidene)succinate (8b): colourless crystals; mp 60–64 °C (*i*-hexane–EtOAc); R_f 0.13 (PE–EtOAc, 10:1). IR ($CDCl_3$): 2957, 2871, 1717 (C=O), 1429, 1305, 1219, 1166, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.39 (m, 6 H), 7.18–7.23 (m, 4 H), 3.45 (s, 6 H), 2.53 (m, 4 H), 1.18–1.32 (m, 8 H), 0.83 (t, 6 H, *J* = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0 (C), 154.0 (C), 141.2 (C), 128.0 (CH), 127.3 (CH), 127.1 (CH), 126.5 (C), 51.5 (Me), 36.1 (CH_2), 29.1 (CH_2), 22.9 (CH_2), 13.9 (Me). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{34}O_4Na$: 457.2349; found: 457.2368.

(2*E*,3*E*)-Diethyl 2,3-di(hexan-2-ylidene)succinate (8c): colourless oil; R_f 0.37 (PE–EtOAc, 10:1). IR ($CDCl_3$): 2957, 2927, 2867, 1709 (C=O), 1613 (C=C), 1459, 1206, 1092, 1039 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.11 (q, 4 H, *J* = 7.1 Hz), 2.13 (s, 6 H), 2.04 (br s, 4 H), 1.32–1.40 (m, 4 H), 1.22–1.29 (m, 4 H), 1.21 (t, 6 H, *J* = 7.1 Hz), 0.86 (t, 6 H, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C), 152.7 (C), 125.2 (C), 59.8 (CH_2), 37.0 (CH_2), 29.1 (CH_2), 22.8 (CH_2), 19.7 (Me), 14.2 (Me), 13.9 (Me). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{34}O_4Na$: 361.2349; found: 361.2348.

(2*E*,3*E*)-Diethyl 2,3-bis(2-methylpropylidene)succinate (8d): yellow oil; R_f 0.28 (PE–EtOAc, 10:1). IR ($CDCl_3$): 2963, 2872, 1712 (C=O), 1231, 1038, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, 2 H, *J* = 10.7 Hz), 4.15 (q, 4 H, *J* = 7.1 Hz), 2.35 (m, 2 H), 1.22 (t, 6 H, *J* = 7.1 Hz), 0.96 (m, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6 (C), 151.9 (CH), 125.2 (C), 60.6 (CH_2), 29.0 (CH), 21.4 (Me), 14.2 (Me). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{26}O_4Na$: 305.1723; found: 305.1708.

(2*Z*,3*Z*)-Dimethyl 2,3-bis(1-phenylethylidene)succinate (8e): white amorphous solid; R_f 0.04 (PE–EtOAc, 10:1). IR ($CDCl_3$): 2950, 1712 (C=O), 1433, 1221, 1199, 1043, 907, 720, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.29 (m, 10 H), 3.37 (s, 6 H), 2.10 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C), 149.8 (C), 142.5 (C), 128.0 (CH), 127.5 (CH), 127.1 (C), 126.5 (CH), 51.4 (Me), 23.0 (Me). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}O_4$: 351.1596; found: 351.1601.

Diethyl 2,3-di(propan-2-ylidene)succinate (8f): colourless oil; R_f 0.31 (PE–EtOAc, 10:1). IR ($CDCl_3$): 2982, 2911, 1709 (C=O), 1625 (C=C), 1444, 1220, 1076 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.12 (q, 4 H, *J* = 7.1 Hz), 2.16 (s, 6 H), 1.72 (s, 6 H), 1.22 (t, 6 H, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.4 (C), 149.1 (C), 125.7 (C), 59.9 (CH_2), 23.7 (Me), 22.1 (Me), 14.2 (Me). LCMS (ES+): *m*/*z* = 255 [M + H]$^+$. Spectroscopic data were consistent with the literature values.[18]

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