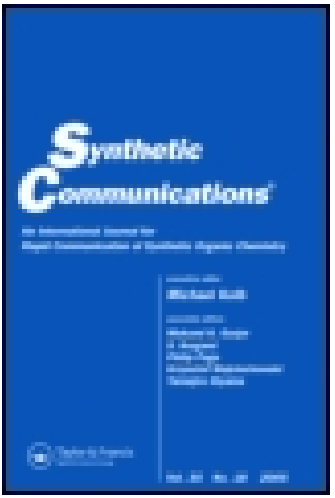

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Synthesis of Resorcinols via a Michael Addition-Dieckman Cyclization Sequence of Dimethyl 1,3-Acetonedicarboxylate Anion with Alkyl Alkynoates

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SYNTHESIS OF RESORCINOLS VIA A MICHAEL ADDITION-DIECKMAN CYCLIZATION SEQUENCE OF DIMETHYL 1,3-ACETONEDICARBOXYLATE ANION WITH ALKYL ALKYNOATES.

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Abstract: The reaction of dimethyl 1,3-acetonedicarboxylate anion **1** with a number of alkyl alkynoates gives unsymmetrical (from alkynoates **2a-g**) or symmetrical (from alkynoates **2h-i**) resorcinols, in a one pot synthesis.

The resorcinols have great significance in synthetic chemistry,[1] because numerous biologically active and naturally ocurring compounds have this system in their framework.[2] We report herein a mild, one pot, regiocontrolled route for unsymmetrical and symmetrical resorcinols (**3a-e** and **4h-i**, respectively) employing a tandem Michael addition[3] of dimethyl 1,3-acetonedicarboxylate anion to alkyl alkynoates **2a-i**, followed by an *in situ* Dieckmann cyclization[4] through enolate intermediates. Although the reaction of dimethyl 1,3-acetonedicarboxylate with alkyl alkynoates has been described,[5] under the specified conditions (in general more vigorous conditions than those reported here) only unsymmetrical resorcinols of type **3** were obtained. Analogous reactions with alkynones[6] and alkynals[7] have also been reported.

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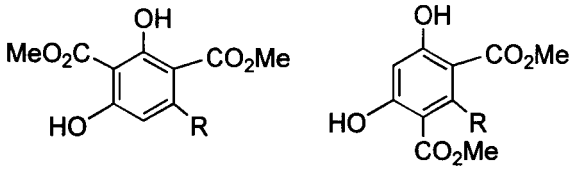
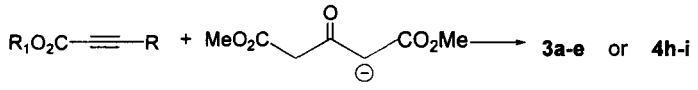


fig. 1

The reactions were carried out with the sodium salt of dimethyl 1,3-acetonedicarboxylate 1 (formed with NaH), and the alkyl alkynoate in dry THF at the indicated temperature (see table 1), affording the unsymmetrical resorcinols **3a-e** from the acetylenic esters **2a-g** and the symmetrical resorcinols **4h-i** from the methyl alkynoates **2h-i** (Scheme 1) in moderate to good yields.



2a-i **1**

a, R=R$_1$=Me
b, R=C$_6$H$_5$, R$_1$=Me
c, R=CH$_2$OBz, R$_1$=Me
d, R=CH$_2$OPv, R$_1$=Me
e, R=CH$_2$OTHP, R$_1$=Me
f, R=CH$_2$OTHP, R$_1$=iPr
g, R=CH$_2$OTHP, R$_1$=tBu
h, R=H, R$_1$=Me
i, R=CO$_2$Me, R$_1$=Me

Scheme 1

It is interesting to notice that the temperature plays an important role for the reactions with different alkyl alkynoates, depending on the substituent in the β-acetylenic carbon. The results and conditions are summarized in Table 1.

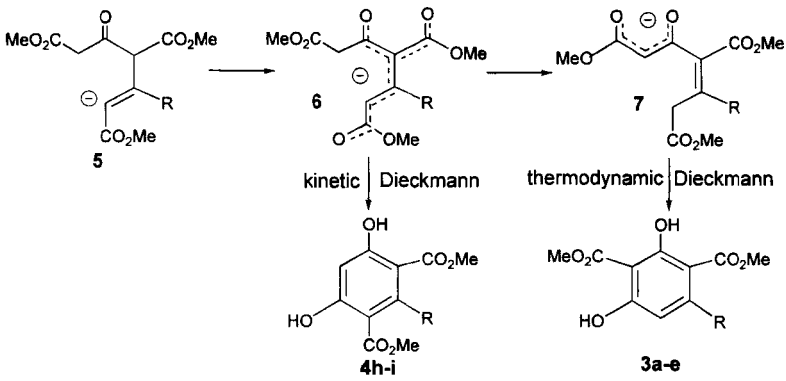
Thus, with the methyl alkynoate **2b** there was no reaction at 25 °C, but at 40 °C took place in 12 hours and at 55 °C was complete in 3.5 hours. When alkyl alkynoates **2a**, **2c-g**

Table 1

Entry	Alkynoate	Product	T(°C)	t(h)	Yield (%)
1	2a	3a	25	2	59
2	2b	3b	40	12	78
3	2b	3b	55	3.5	84
4	2c	3c	25	2	55
5	2d	3d	25	2	67
6	2e	3e	25	2	48
7	2f	3e	25	2	44
8	2g	3e	25	2	42
9	2h	4h	−10	2	18
10	2i	4i	−10	2	22
11	2i	4i	−40	2	34

were treated at −10 °C, the unsymmetrical resorcinols **3a-e** were obtained, but the reaction time was longer and the yield decreased. On the other hand, with more reactive acceptors such as methyl propiolate **2h** or dimethyl acetylendicarboxylate **2i**, the reaction afforded only polymers at 25 °C, probably due to an anionic polymerization. In these cases, the symmetrical resorcinols **4h** and **4i** were prepared at -10 °C, and when the reaction was carried out at -40 °C, the yield increased in the case of dimethyl acetylenedicarboxylate **2i**. This suggests that the reactivity of the alkynoate and the type of substituent on the β-acetylenic carbon defines the site selectivity in the Dieckmann cyclization resulting in the formation of **3** or **4**. A plausible mechanism of this event is shown in Scheme 2.

The vinyl carbanion **5**, initially formed by Michael addition of the dimethyl 1,3-acetonedicarboxylate enolate to the methyl alkynoate, is rapidly protonated by the more acidic methine proton to give carbanion **6**, precursor of the symmetrical resorcinols **4h-i**. In spite of its apparent stability, the highly crowded environment of this intermediate, allows its isomerization (at higher temperatures) to enolate **7**, precursor of the non



Scheme 2

symmetrical resorcinols **3a-e**. We suggest that the delocalized anion **6** is kinetically formed from **5** and is stable at low temperatures (below 0 °C), but isomerizes to the thermodynamic (less crowded) enolate above room temperature; hence, in the cases where low temperatures were neccesary to avoid polymerization of the alkynoate, enolate 5 is cyclized to the symmetrical resorcinols **4h-i**. If our proposal is correct, we have an example of an enolate **6** which can not delocalize efficiently the negative charge (compared to **7**) in the neighbouring appropriate located groups by steric reasons. We hope to find in a near future the right experiments to support or discredit our hypothesis.[8]

Finally, we have also found that bulky substituents in the carboalkoxy part of the alkynoates does not avoid (or deviate) the Dieckmann cyclization step, since the *isopropyl* and *tert*-butyl esters **2f** and **2g** cyclizes equally well to give **3e**, as the methyl ester **2e** does.

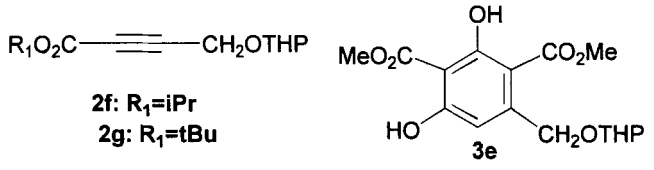


fig. 2

In conclusion, this research provides a short and efficient method for the synthesis of symmetrical and unsymmetrical substituted resorcinols from aliphatic substrates.

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Experimental Section

All reactions were carried out under an argon atmosphere. Tetrahydrofuran was freshly distilled over benzophenone-sodium. The required substrates **2a**, **2b**, **2h** and **2i** and dimethyl 1,3-acetonedicarboxylate were purchased from Aldrich Inc. **2c** And **2d** were prepared from 2-butyn-1,4-diol in ≈ 48% overall yield in three steps, *i. e.*, monoprotection with BzCl and PvCl respectively in pyridine/CH_2Cl_2[9], followed by oxidation with the Jones reagent[10] and esterification with CH_2N_2[11]. **2e**, **2f** And **2g** were synthesized by deprotonation of 3-(tetrahydropyranyloxy)-1-propyne[12] with n-BuLi followed by carboalkoxylation with methyl chloroformate, *isopropyl* chloroformate and di-*tert*-butyl dicarbonate respectively[13].

Melting points are uncorrected. TLC was conducted on precoated Kieselgel 60 F_{254} (Art. 1.05554; Merck) aluminum sheets and visualized by UV irradiation, column chromatography was carried out using silica gel (70-230 mesh). IR spectra were run on KBr discs or thin films. ^{1}H NMR spectra were recorded either at 200 or 300 MHz, while ^{13}C NMR spectra were run at 75 MHz. Low-and high-resolution mass spectra were measured at 70 eV (EI). Elemental analysis were performed by Galbraith Laboratories, Inc.

General Procedure for the Preparation of Dimethyl 2,4-dihydroxybenzene-1,3-dicarboxylate derivatives (3a-e) and Dimethyl 2,4-dihydroxybenzene-1,5-dicarboxylate derivatives (4h-i).

Dimethyl 1,3-acetonedicarboxylate (97%; 0.4g, 2.22 mmol) was added dropwise to a suspension of NaH (60%; 0.12g, 3 mmol) in dry THF (4ml) with magnetic stirring. The resulting solution was heated, cooled or maintained at *r.t.* according to the alkyl alkynoate used and this was finally added (2.22 mmol); the reaction mixture was then stirred for the stated period (Table 1). The mixture was poured into dilute HCl (15 ml), the organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine (15ml), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography, the resorcinol being eluted with 3% ethyl acetate in hexanes.

Dimethyl 2,4-dihydroxy-6-methylbenzene-1,3-dicarboxylate (3a): yield 59%, mp 103-105 °C; IR (KBr) 2437, 1662, 1257 cm^{-1}; ^1H NMR δ ppm 2.45 (s, 3H), 3.93 (s, 3H), 4.01 (s, 3H), 6.35 (s, 1H), 11.63 (s, 1H), 12.68 (s, 1H); ^{13}C NMR δ ppm 23.87, 52.12, 52.68, 99.66, 106.77, 111.95, 148.56, 164.89, 165.69, 171.05, 171.38; MS (EI) *m/z* (relative intensity) 240 (M^+, 55), 208 (94), 176 (100), 150 (34), HRMS calcd. for $C_{11}H_{12}O_8$ 240.0634, found 240.0635. Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.00. Found: C, 55.13; H, 5.15.

Dimethyl 2,4-dihydroxy-6-phenylbenzene-1,3-dicarboxylate (3b): yield 84%, mp 127-128 °C (lit.[7] mp 126-128 °C); IR (KBr) 3440, 1663, 1563, 1254 cm^{-1}; ^1H NMR δ ppm 3.52 (s, 3H), 4.07 (s, 3H), 6.49 (s, 1H), 7.25-7.45 (m, 5H), 11.01 (s, 1H), 11.53 (s, 1H); ^{13}C NMR 51.84, 52.96, 99.72, 108.94, 111.14, 127.53, 127.97. 128.06, 140.62, 150.29, 162.04, 163.87, 169.59, 170.47; MS (EI) *m/z* (relative intensity) 302 (M^+, 63), 238 (100), 270 (73), 212 (12); HRMS calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0787. Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.63. Found: C, 63.94; H, 4.89.

Dimethyl 2,4-dihydroxy-6-(benzoyloxymethyl)benzene-1,3-dicarboxylate (3c): yield 55%, mp 113-114 °C; IR (KBr) 3427, 1724, 1664, 1258 cm^{-1}; ^1H NMR δ ppm 3.95 (s, 3H0, 4.03 (s, 3H), 5.58 (s, 2H), 6.73 (s, 1H), 7.42-7.70 (m, 3H), 8.10-8.20 (m, 2H), 12.05 (s, 1H), 13.00 (s, 1H); ^{13}C NMR δ ppm 52.37, 52.64, 64.90, 100.93, , 103.44, 108.09, 128.38, 129.56, 133.16, 145.72, 165.56, 165.78, 167.90, 170.69, 170.82; MS (EI) *m/z* (relative intensity) 360 (M^+, 39), 328 (29), 223 (48), 105 (100); HRMS calcd for $C_{18}H_{16}O_8$ 360.0845, found 360.0836. Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.55; H, 4.44. Found: C, 60.35; H, 4.50.

Dimethyl 2,4-dihydroxy-6-(pivaloyloxymethyl)benzene-1,3-dicarboxylate (3d): yield 67%; mp 140-142 °C; IR (KBr) 3341, 1730, 1639, 1525 cm^{-1}; ^1H NMR δ ppm 1.28 (s, 9H), 3.94 (s, 3H), 4.02 (s, 3H), 5.30 (s, 2H), 6.61 (s, 1H), 11.96 (s, 1H), 12.88 (s, 1H); ^{13}C NMR δ ppm 27.28, 39.00, 52.81, 52.81, 64.64, 101.01, 103.43, 108.15, 146.26, 165.78, 167.14, 170.95, 171.01, 177.85; MS (EI) *m/z* (relative intensity) 340 (M^+, 33), 308 (31), 224 (88), 57 (100); HRMS calcd for $C_{16}H_{20}O_8$ 340.1158, found 340.1154. Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.88. Found: C, 56.77; H, 5.96.

Dimethyl 2,4-dihydroxy-6-(tetrahydropyranyloxymethyl)benzene-1,3-dicarboxylate (3e): yield 48%, mp 72-73 °C; IR (KBr) 2956, 1741, 1659,1525 cm^{-1}; ^1H NMR δ ppm 1.45-1.95 (m, 6H), 3.50-3.60 (m, 2H), 3.93 (s, 3H), 4.02 (s, 3H), 4.73 (m, 1H), 4.81 (AB sys, J= 13.6 Hz, 2H), 6.87 (s, 1H), 11.79 (s, 1H), 12.71 (s, 1H); ^{13}C NMR δ ppm 19.19, 25.39, 30.46, 48.65, 52.29, 52.70, 62.05, 67.21, 98.26, 100.28, 102.26, 107.79, 149.25, 165.10, 166.74, 171.02; MS (EI) (relative intensity) 340 (M^+, 2), 240 (76), 208 (100), 85 (53). Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.47; H, 5.88. Found: C, 56.65; H, 5.84.

Dimethyl 2,4-dihydroxybenzene-1,5-dicarboxylate (4h): yield 18%; mp 146-148 °C (lit.[14] 147-148 °C); IR (KBr) 3414, 1684, 1602, 1318 cm^{-1}; ^1H NMR δ ppm 3.95 (s, 6H),

6.48 (s, 1H), 8.42 (s, 1H), 11.25 (s, 2H); ^{13}C NMR δ ppm 52.34, 104.19, 105.72, 134.16, 167.07, 169.75; MS (EI) (relative intensity) 226 (M^+, 60), 194 (100), 162 (94), 134 (32). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.09; H, 4.42. Found: C, 53.24; H, 4.59.

Trimethyl 4,6-dihydroxybenzene-1,2,3-tricarboxylate (4i): yield 34%; mp 128-129 °C; IR (KBr) 3057, 1742, 1728, 1679 cm^{-1}; ^{1}H NMR δ ppm 3.91 (s, 9H), 6.58 (s, 1H), 11.73 (s, 2H); ^{13}C NMR δ ppm 52.58, 53.24, 105.60, 128.38, 140.17, 166.81, 167.91, 168.89; MS (EI) relative intensity) 284 (M^+, 100), 252 (85), 220 (71), 192 (35); HRMS calcd for $C_{12}H_{12}O_8$ 284.0532, found 284.0527. Anal. Calcd for $C_{12}H_{12}O_8$: C, 50.70; H, 4.22. found: C, 51.02; H, 4.51.

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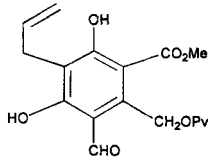
8. After the present paper was written, we found that diminishing the acidic character of the second proton participating in this process (by the introduction of an allylic group in dimethyl 1,3-acetonedicarboxylate), we obtained the resorcinol **7** from the kinetic enolate in 28% yield and the diastereoisomeric alcohols **8** from the thermodynamic enolate in 63% yield, using 4-pivaloyloxy-2-butynal as Michael acceptor.[7]



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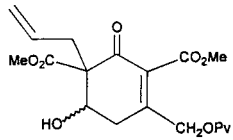

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