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FACILE SYNTHESIS OF (E)-4-ARYL-2-METHYL-3-BUTENOIC ACIDS AND THEIR METHYL ESTERS BY THE CONDENSATION OF TIGLIC ACID DIANION WITH ARYNES

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Abstract

The condensation of various arynes with tiglic acid dianion yields (E)-4-aryl-2-methyl-3-butenoic acids exclusively, after proton quench. These acids were characterized as their methyl esters, which were prepared by treating the acids with diazomethane.

We[1] showed recently that 2-butenoic acid (crotonic acid) dianion when treated with methoxy-substituted arynes underwent γ-arylation exclusively, presumably by the usual aryne arylation mechanism, to yield mainly (E)-4-aryl-3-butenoic acids and minor amounts of (E)-4-aryl-2-butenoic acid, after proton quench. In contrast, 2-butenoic acid dianion reacted with 3,6-dimethylbenzyne to yield 5,8-dimethyl-2-tetralone via the tandem addition-rearrangement pathway.[2]

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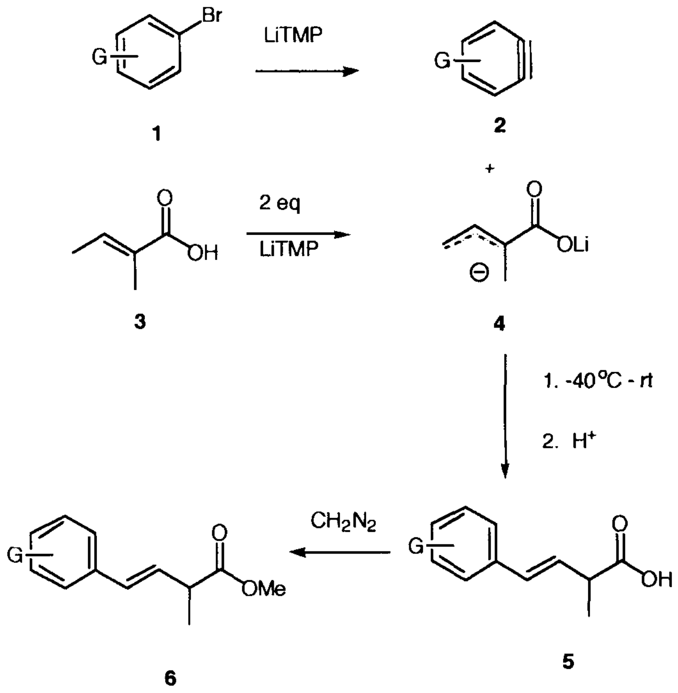
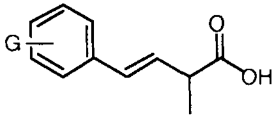
Scheme 1

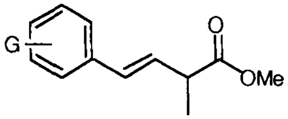


We report herein that arynes (**2 a-f**) react with tiglic acid (2-methyl-2-butenoic acid) dianion (**4**) at -40 °C to give (E)-4-aryl-2-methyl-3-butenoic acids (**5 a-f**) exclusively in 75-56% yields (Scheme 1). The reactants **2a-f** and **4** were prepared by treating haloarenes (**1 a-f**) and tiglic acid (**3**), respectively, with lithium 2,2,6,6-tetramethylpiperidide (LiTMP). The yields of **5a-f** were estimated from the integration of the phenyl (**5 a**) or the aryl methoxy signals of the 4-arylated acids (**5b-f**) and the 4-methyl resonance of tiglic acid (**3**) that were revealed in the ^{1}H NMR spectra of the crude reaction mixtures.

Table 1. Yields (%) of (E)-4-Aryl-3-butenoic acid (**5**) and Methyl (E) 4-Aryl-3-butenoate (**6**)



5



6

	G	Yield (%) Acid (**5**)^{a}	 Ester (**6**)^{b}
a	H	75	66
b	3-methoxy	72	68
c	2,5-dimethoxy	59	56
d	3,4-dimethoxy	56	52
e	3,4,5-trimethoxy	50	48
f	5-methoxy-2-methyl	70	68

a. Yields estimated from integration of phenyl (**5 a**) or methoxyphenyl signals of **5 b-f** and 4-methyl signal of tiglic acid (**3**) revealed in the ^{1}H NMR spectra of the crude reaction mixtures.

b. Yields given as total yields based on tiglic acid (**3**).

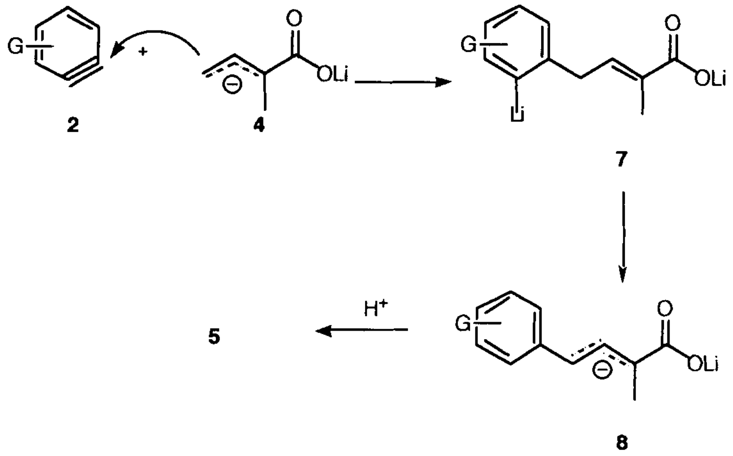
Since these highly viscous acids proved difficult to separate, they were converted to their methyl esters (**6 a-f**) by treatment with diazomethane in ca. 95% yield. Thus the overall yield of **6 a-f** from the two-step reaction ranged from 68% to 48%. The results for the individual acids (**5 a-f**) and esters (**6 a-f**) are listed in Table 1.

The proposed structures of the esters (**6 a-f**) were consistent with their IR spectra, which revealed characteristic *trans* absorption bands around 970 cm^{-1}, with their ^1H NMR spectra, which revealed typical splitting patterns for a $CH=CH-CH_3$ system and *trans* coupling constants (J = 16 Hz), and with their ^{13}C NMR spectra, which reveal ester carbonyl signals at δ 174-175 ppm. Careful examination of IR and ^1H NMR spectra of the crude reaction mixtures revealed the absence of 2-aryl-2-methyl-2-butenoic acids of 4-aryl-2-methyl-2-butenoic acids. These results are in contrast to those observed for the alkylation of tiglic acid which undergoes predominantly α-alkylation to give 2-alkyl-2-methyl-3-butenoic acids plus minor amounts of γ-alkylation to give (Z)-4-alkyl-2-methyl-2-butenoic acids under comparable temperatures.[3] Apparently the steric effect of the 2-methyl group in tiglic acid mitigates against α-arylation.[4]

A possible mechanism to account for the formation of acids (**5**) is shown in Scheme 2. Accordingly, the *exo* (or *s-cisoid*) conformer of **4** adds to the aryne (**2**) affording adduct (**7**), which is subsequently converted to the *exo* conformer of the 4-arylated dianion (**8**). Protonation of **8** thus affords acid **5**. Although it might be expected that *endo* and *exo* geometries of these dianions (**4** and **8**) equilibrate somewhat rapidly in solution, this apparently is not the case here since a mixture of E and Z acids would be expected.[5]

These 4-aryl-2-methyl-3-butenoic acids and esters should prove to be

Scheme 2



synthetically useful building blocks for the construction of 2-methyl-1-tetralones.

Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (200 MHz) spectra were obtained in CDCl$_3$, and the chemical shifts were related to TMS. Unless otherwise indicated, reagents were purchased from Aldrich and used without further purification. Merck silica gel 9385 (230-400 mesh) was used for flash chromatography. THF and 2,2,6,6-tetramethylpiperidine were refluxed over blue sodium-benzophenone ketyl, followed by distillation prior to use.

General Procedure For The Synthesis of Methyl (E)-4-Aryl-2-methyl-3-

butenoates (**6a-f**). LiTMP (30 mmol) was freshly prepared by adding *n*-BuLi (12 ml of 2.5 M in hexanes, 30 mmol) to a stirred solution of 2,2,6,6-tetramethylpiperidine (460 mg, 30 mmol) in THF (50 ml) at room temperature, under a N_2 atmosphere. After 10 min, tiglic acid (**3**,100 mg, 10 mmol) in THF (25 ml) was added over a period of 10 min, and the resulting solution was stirred for an additional 10 min then cooled to -40 °C. The haloarene (**1**, 10 mmol) in THF (25 ml) was then slowly added (5 min) during which time the solution developed a dark reddish hue. The resulting solution was stirred another 20 min at -40 °C, then allowed to warm slowly (ca. 1 h) to room temperature. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution, and concentrated (rotary evaporator). The remaining material was extracted with CH_2Cl_2 (3 X 50 ml) and the extracts were combined, washed (brine), dried (sodium sulfate), and concentrated (rotatory evaporator) to yield a viscous mixture of tiglic acid (**3**) and (E)-4-aryl-2-methyl-3-butenoic acid (**5a-f**).

The acids (**5a-f**) were then dissolved in ether (25 ml) and treated with excess CH_2N_2 at -30 °C. The CH_2N_2 was prepared by adding a 10% aqueous KOH solution to a solution of Diazald in ether and diethoxyethane at 70°C KOH, and distilling the CH_2N_2 into a cold (-30 °C) receiver. The reaction mixture was allowed to warm to room temperature, then stirred for an additional 30 min. The excess CH_2N_2 was removed by the addition of acetic acid and the remaining solution was concentrated (rotary evaporator) to yield the crude ester (**6 a-f**), which was purified by column chromatography using acetone-hexane mixture (5:95 to 10:90, respectively) as eluent. The physical and spectral properties of **6a-f** are given below.

Methyl 2-methyl-4-phenyl-3-butenoate (**6 a**): ^{1}H NMR ($CDCl_3$) δ 1.30 (d, *J* = 7 Hz, 3 H), 3.30 (m, 1 H), 3.57 (s, 3 H), 6.25 (dd, *J* = 7, 16 Hz, 1 H), 6.46 (d, *J* = 16 Hz, 1 H), 7.16-7.52 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.25, 42.98, 51.72, 126.14, 127.40, 128.40, 128.61, 131.08, 136.80, 174.70; IR (neat) ν_{max} 1736, 1599, 965 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.96; H, 7.42. Found: C,76.04; H, 7.49.

Methyl 4-(3'-methoxyphenyl)-2-methyl-3-butenoate (**6 b**): ^{1}H NMR ($CDCl_3$) δ 1.35 (d, *J* = 7 Hz, 3 H), 3.30 (m, 1 H), 3.66 (s, 3 H), 3.79 (s, 3 H), 6.29 (dd, *J* = 7, 16 Hz, 1 H), 6.44 (d, *J* = 16 Hz, 1 H), 6.77 (m, 2 H), 6.88 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.45, 43.02, 51.82, 55.12, 111.60, 113.28, 114.40, 129.01, 129.44, 124.57, 159.85, 174.80; IR (neat) ν_{max} 1736, 1598, 968 cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.98; H, 7.29.

Methyl 4-(2',5'-dimethoxyphenyl)-2-methyl-3-butenoate (**6 c**): ^{1}H NMR ($CDCl_3$) δ 1.35 (d *J* = 7 Hz, 3 H), 3.35 (m, 1 H), 3.65 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 6.24 (dd, *J* = 8, 16 Hz, 1 H), 6.67-6.89 (m, 3 H), 6.98 (d, *J* = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.39, 43.42, 51.69, 55.51, 56.07, 111.94, 112.28, 113.64, 125.76, 126.67, 129.35, 151.05, 153.09, 174.93; IR (neat) ν_{max} 1735, 1607, 972 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.48: H, 7.25. Found: C, 67.55; H, 7.22.

Methyl 4-(3',4'-dimethoxyphenyl)-2-methyl-3-butenoate (**6 d**): ^{1}H NMR ($CDCl_3$) δ 1.33 (d, *J* = 7 Hz, 3 H), 3.27 (m, 1 H), 3.53 (s, 3 H), 3.65 (s, 3 H), 3.72 (s, 3 H), 6.16 (dd, *J* = 8, 16 Hz, 1 H), 6.39 (d, *J* = 16 Hz, 1 H), 6.66-6.69 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 17.34, 42.89, 51.65, 55.51, 108.82, 111.20, 119.39, 126.62, 129.92, 130.74, 149.02, 174.88; IR (neat) ν_{max} 1734, 1514, 966 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.48: H, 7.25. Found: C, 67.59; H, 7.30.

Methyl 4-(3',4',5'-trimethoxyphenyl)-2-methyl-3-butenoate (**6 e**): ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 7 Hz, 3 H), 3.28 (m, 1 H), 3.69 (s, 3 H), 3.76 (s, 3 H), 3.84 (s, 6 H), 6.15 (dd, J = 8, 16 Hz, 1 H), 6.38 (d, J = 16 Hz, 1 H), 6.56 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.33, 42.89, 51.76, 56.01, 60.70, 103.56, 128.05, 131.04, 132.48, 137.97, 140.10, 153.27, 174.75; IR (neat) ν_{max} 1734, 1582, 966 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27: H, 7.19. Found: C, 64.33; H, 7.25.

Methyl 4-(5'-methoxy-2'-methylphenyl)-2-methyl-3-butenoate (**6f**): ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 7 Hz, 3 H), 2.26 (s, 3 H), 3.28 (m, 1 H), 3.67 (s, 3 H), 3.79 (s, 3 H), 6.24 (dd, J = 8, 16 Hz, 1 H), 6.67-7.01 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 17.47, 20.35, 43.50, 51.68, 55.50, 118.94, 125.94, 127.18, 128.86, 129.66, 154.60, 175.05; IR (neat) ν_{max} 1734, 1582, 966 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.18; H, 8.22.

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References

1. Deshmukh, A. R.; Tran, L.; Biehl, E. R. *J. Org. Chem.* **1992**, *57*, 667.
2. Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.
3. Cainelli, G.; Cardillo, G.; Contento, M.; Umani-Ronchi, A. *Gazz. Chim. Ital.* **1974**, *104*, 625.
4. For a good account of regioselectivity trends exhibited by unsaturated carboxylic acid dianions, see: Aurell, M. J.; Gil, S.; Maestres, R.; Parra, M.; Tortajada, A. *Tetrahedron,* **1994**, *50*, 5109, and references therein.

5. For example, Pfeffer and Silbert showed that alkylation of *cis* -and *trans* -2-hexenoic acid dianions gave mixtures of *trans* and *cis/trans* mixtures of 3-hexenoic acids, respectively. Pfeffer, P. E.; Silbert, P. E. *J. Org. Chem.* **1971**, *36*, 3290.

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