Synthesis of β-Dicarbonyl Compounds *via* the Conjugate Addition of Benzaldoximate Anion to α,β-Acetylenic Carbonyl Compounds†

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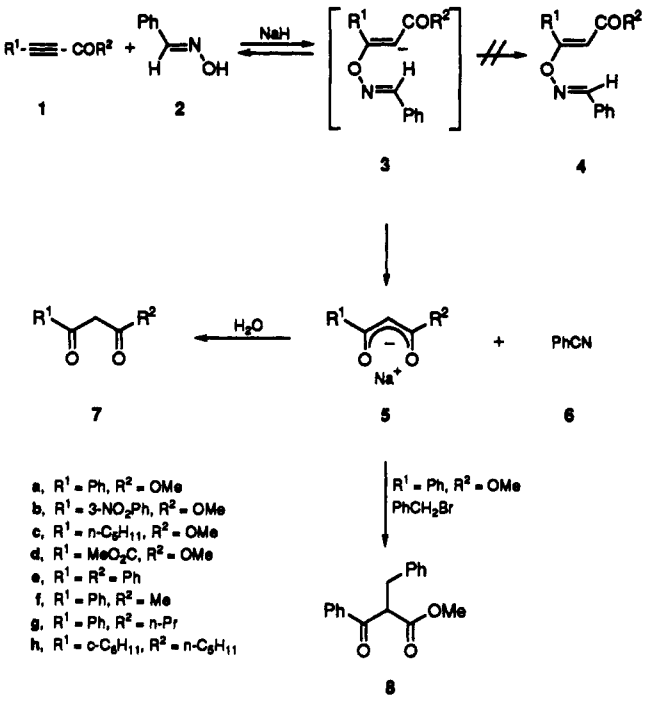
We recently required a method for the conversion of α,β-acetylenic carbonyl compounds into the corresponding β-dicarbonyl compounds. The transformation of α,β-acetylenic esters into β-keto esters (acids) has previously been accomplished by hydration with alcoholic hydroxide[1,2] or, much more efficiently, by acidic hydrolysis of the acetylene–secondary amine adducts.[2-6] The considerable nucleophilicity of oxime anions[7,8] coupled with the facile reduction of the N–O bond of oxime ethers[9] as well as the easy base-induced cleavage of *O*-alkylaldoximes[8] suggested that β-dicarbonyl compounds ought to be preparable via the conjugate addition products of oxime anions to α,β-acetylenic carbonyl compounds. This paper demonstrates that such a supposition is indeed correct.

The viability of the above concept was studied using *syn*-benzaldoxime (**2**, Scheme 1) and methyl phenylpropionate (**1a**) as the acetylenic carbonyl component. Reaction of this acetylene with 1 equiv of *syn*-benzaldoxime, containing 5 mol % of sodium benaldoximate, in various solvents and at various temperatures (0–80 °C) did not give any of the expected oxime–acetylene adduct **4**. Traces (<5%) of the β-keto ester **7a** were, however, isolated after aqueous workup. When a full equivalent of the oximate anion was used at room temperature (or below), **7a** as well as benzonitrile (**6**),[10] i.e., the base-induced fragmentation products of **4**, were generated in substantial amounts. The rate and extent of this reaction were dependent on the nature of the solvent and on the oxime stereochemistry. In THF or methanol, **7a** could be isolated in *ca.* 30% yield after 36–48 h. In contrast, the reaction was nearly

Scheme 1



instantaneous at room temperature in solutions containing dipolar aprotic solvents such as DMSO or DMF, with a 1:2 dioxane–DMF solution or pure DMSO giving optimal yields of **7a** (*ca.* 80%, Table 1) in 0.5 h. Under the same conditions (dioxane–DMF, 0.5 h), *anti*-benzaldoximate gave *ca.* 20% of **7a** (70% recovery of starting materials), and the reaction did not advance even after 2 h.

The conditions which were optimal for the generation of **7a** were then utilized for the synthesis of several other β-keto esters and for the conversion of α,β-acetylenic ketones to β-diketones (Table 1). Under these conditions, dimethyl acetylenedicarboxylate (**1d**) and methyl propiolate (**9**) were converted into complex mixtures. However, in THF as the solvent the diester **1d** was transformed into dimethyl oxalacetate (**7d**) in *ca.* 40% yield[10] at −20 °C, while the (*E*)-oxime–acetylene adduct **10** (Scheme 2) was obtained in 35% yield from the monoester **9** at room temperature.[11]

With regard to the mechanism of formation of the β-dicarbonyl compounds, we suggest a fast (probably reversible) addition of *syn*-benzaldoximate to the activated acetylene to give the vinyl anion **3**, followed by a rapid (especially in dipolar aprotic solvents) intramolecular fragmentation of this species to the enolate **5** and benzonitrile (Scheme 1). As expected, the enolate **5** can be trapped as demonstrated by the isolation of **8** (85% yield) upon addition of benzyl bromide. The isolation of the ethyl propiolate–*syn*-benzaldoxime adduct **10** (Scheme 2) and the facile fragmentation thereof to the enolate **11** with sodium hydride in DMF support the above mechanistic proposal. The presence of **11** was established by alkylation with benzyl bromide to give a chromatographically inseparable 4:1 mixture of (*E*)-methyl 3-(benzyloxy)-acrylate (**12**) and its α-benzyl congener **13**. Predominant O-alkylation is a well-recognized characteristic of such

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(1) Moureau, C.; Delange, R. *Compt. Rend.* **1903**, *136*, 753.
(2) Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3628.
(3) Moreau, C.; Lagennec, I. *Bull. Soc. Chim. Fr.* **1906**, *35*, 1190.
(4) Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634.
(5) Bestmann, H. J.; Beismann, C. *Liebigs Ann. Chem.* **1977**, 282.
(6) Presumably, these compounds could also be obtained by alcoholysis of the readily prepared (Miller, L. A. U.S. Patent 3, 129,201, 1964; *Chem. Abstr.* **1964**, *61*, 9405f) carboxylic acid–acetylenic ester adducts.
(7) Metzger, H. In *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed; G. Thieme: Stuttgart, 1968; Vol. 10/4, pp 220–225.
(8) Knudson, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.
(9) Umino, N.; Iwakuma, T.; Ikezaki, M.; Itoh, N. *Chem. Pharm. Bull.* **1978**, *26*, 2897.

(10) The presence of benzonitrile in the product from **1a** and **2** was ascertained by a strong band at 2231 cm^{-1} in the crude product. Benzonitrile was isolated in 57% yield in the reaction of **1d** with benzaldoximate (see Experimental Section).

(11) This stereochemistry was assigned on the basis of an NMR coupling constant of *ca.* 13 Hz for the vinyl protons. *J* values of 12.5 and 7 Hz are reported for the (*E*)- and (*Z*)-methanol–methyl propiolate adducts (Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450).

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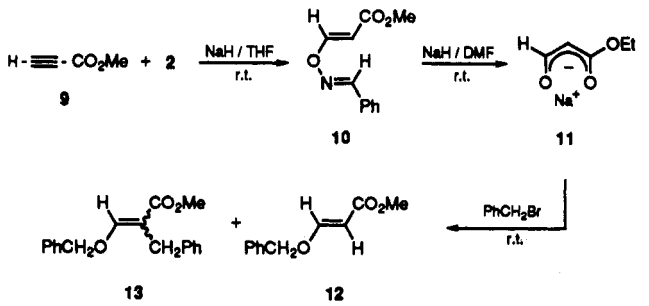
Table 1. Synthesis of β-Dicarbonyl Compounds and Derivatives from α,β-Acetylenic Carbonyl Compounds

acetylene	reaction solvent	product	purification method[a]	purification solvent system	% yield[b]	mp °C/bp found	°C/mm reported
1a	Diox–DMF	7a	CC	Hex–ether (9:1)	82–84	oil	152/15[c]
1a	DMSO	7a	CC	Hex–ether (95:5)	77	oil	
1b	Diox–DMF	7b	CC	Hex–ether (97:3)	68–73	69–70[d]	
1c	Diox–DMF	7c	CC	Hex–ether (85:15)	72–75	oil	oil[e]
1c	DMSO	7c	TLC	Hex–ether–EtOAc (7:3:1)	62	oil	
1d	THF	7d	CC	Hex–ether (92:8)	44	69–71	74[f]
1e	Diox–DMF	7e	CC	Hex–ether (9:1)	83–92	72–73	77–78[g]
1f	Diox–DMF	7f	CC	Hex–ether (9:1)	73–82	49–50	58[h]
1g	Diox–DMF	7g	CC	Hex–ether (85:15)	70–88	oil	oil[i]
1h	Diox–DMF	7h	TLC	Hex–ether (9:1)	70–80	oil	
1h	DMSO	7h	TLC	Hex–ether (9:1)	70	oil	
1a	Diox–DMF	8	CC	Hex–ether (9:1)	85	oil	250–55/50[j]
9	THF	10	CC	Hex–ether (9:1)	35	34–36[k]	

[a] CC = column chromatography on silica gel. TLC = thin-layer chromatography on silica gel. [b] Yield of chromatographically pure material. [c] Reference 20. [d] After crystallization from hexane–ether. [e] Reference 17. [f] Reference 21. [g] Reference 22. [h] Reference 23. [i] ^{1}H NMR spectrum identical to that reported.[24] [j] Reference 25. [k] After crystallization from hexane.

Scheme 2



enolates.[12] The failure of *anti* sodium benzaldoximate to provide **7a** efficiently is also consistent with the above mechanism, since an intermediate related to **3** would be generated with a geometry inappropriate for the intramolecular fragmentation process. The small amount of **7a** which was formed in this case is probably a consequence of partial *anti–syn* isomerization of *anti*-benzaldoxime in DMF solution prior to generation of the configurationally stable oximate. Such isomerizations are known to be rapid for benzaldoximes.[13]

In summary, *syn*-sodium benzaldoximate reacts rapidly with α,β-acetylenic esters and ketones to generate the corresponding β-dicarbonyl compounds as the sodium enolates. Inasmuch as the requisite acetylenic esters[14–17] and ketones[14,18,19] are readily available, this constitutes a useful new route to β-keto esters, β-diketones, and the enolates thereof. In these reactions, *syn*-benzaldoximate functions as a formal OH^- equivalent.

Experimental Section

The physical constants of the compounds described herein were obtained as described previously.[26] The ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$ and are recorded in ppm (δ) from internal TMS. The spectra of compounds with exchangeable hydrogens are those after D_2O exchange.

Dimethyl acetylene dicarboxylate, methyl propiolate, and 4-phenyl-3-butyn-2-one (**1f**) are commercially available. The acetylenic esters[17] **1a** and **1c** and the acetylenic ketones[27] **1e** and **1g** are well-known literature compounds. *Syn*- and *anti* benzaldoximes were prepared as described by Vogel.[28]

Methyl 3-(3-Nitrophenyl)propynoate (1b). Solid 3-(3-nitrophenyl)propynoic acid[29] (2.00 g, 10.5 mmol) was added with stirring to thionyl chloride (0.9 mL, 1.49 g, 12.7 mmol) during the course of 1 h. The excess thionyl chloride was then removed *in vacuo*, and anhydrous methanol (5 mL) was added to the residue at 0 °C. The excess methanol was removed *in vacuo*, and the crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (95:5) to elute **1b** as a solid (1.12 g, 52%) which, on crystallization from hexane–ethyl acetate, had mp 39-41 °C: IR ($CHCl_3$) 2237, 1713, 1537, 1354 cm^{-1}; ^{1}H NMR δ 3.86 (s, 3H), 7.60 (t, 1H, J_o = 8.1 Hz), 7.89 (m, 1H, J_o = 8.1 Hz, J_m = 2.1 Hz), 8.31 (m, ddd, J_o = 8.1 Hz, J_m = 2.1 Hz), 8.44 (t, 1H, J_m = 2.1 Hz); HRMS calcd for $C_{10}H_7NO_4$ 205.0374, found 205.0373.

1-Cyclohexyl-1-octyn-3-one (1h). A solution of 1.5 M methylmagnesium bromide (37.0 mL, 55.5 mmol) in ether was added to a stirred solution of cyclohexylacetylene (4.8 mL, 4.00 g, 37.0 mmol) in anhydrous tetrahydrofuran (100 mL) maintained in an argon atmosphere at 0–5 °C. The solution was then stirred at room temperature for 1 h, after which time freshly distilled *n*-hexanal (6.6 mL, 5.55 g, 55.5 mmol) was added. After 2 h, the reaction was quenched with saturated aqueous ammonium chloride solution, and the product was extracted into ethyl acetate. The extract was dried over sodium sulfate, and the solvent was

(12) Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361.
(13) Le Fevre, R. J. W.; Northcott, J. *J. Chem. Soc.* **1949**, 2235. McCarty, C. G. In *The Chemistry of the Carbon–Nitrogen Double Bond*; Patai, S., Ed.; Interscience Publishers: London, 1970; pp 389–91.
(14) Ziegenbein, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 247–253.
(15) Hall, S. E.; Rousch, W. R. *J. Org. Chem.* **1982**, *47*, 4611. Olomucki, M.; Le Gall, J.-Y.; Barnard, I. *J. Chem. Soc., Chem. Commun.* **1982**, 1290. Hooz, J.; Calzada, J. G.; McMaster, D. *Tetrahedron Lett.* **1985**, *26*, 271. Taschner, M. J.; Rosen, T.; Heathcock, C. H. *Org. Synth.* **1985**, *64*, 108. Olomucki, M.; Le Gall, J.-Y. *Org. Synth.* **1987**, *65*, 47. Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941. Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378. Camps, F.; Coll, J.; Llebaria, A.; Moreto, J. M.; Ricart, S. *Synthesis* **1989**, 122.
(16) Earl, R. A.; Townsend, L. B. *Org. Synth.* **1981**, *60*, 81. Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889.
(17) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849. Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800.
(18) Reference 13, pp 219–225. Fatiadi, A. *Synthesis* **1976**, 65.
(19) Schmidt, U.; Schwochau, M. *Chem. Ber.* **1964**, *97*, 1649. Normant, J. F.; Bourgain, M. *Tetrahedron Lett.* **1970**, 2659. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. Kawanami, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5131. Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.* **1984**, *25*, 2411. DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309.
(20) Wahl, A. *Compt. Rend.* **1908**, *147*, 72.
(21) Hantzsch, A. *Chem. Ber.* **1915**, *48*, 1407.
(22) Allen, C. F. H.; Abell, R. D.; Normington, J. B. *Organic Syntheses*; Wiley: New York, 1956; Collect. Vol. 1, p 205.
(23) Muir, W. M.; Richie, P. D.; Lyman, D. J. *J. Org. Chem.* **1966**, *31*, 3790.
(24) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.
(25) *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: London, 1982; Vol. 1, pp 598–9 (B-00692).
(26) Guzmán, A.; Quintero, C.; Muchowski, J. M. *Can. J. Chem.* **1991**, *69*, 2059.
(27) Nightingale, D. V.; Wadsworth, F. *J. Am. Chem. Soc.* **1945**, *67*, 416.
(28) Vogel, A. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Langman Scientific & Technical: Essex, 1978; p 810.
(29) Reich, S.; Koehler, S. *Ber.* **1913**, *46*, 3727.

removed *in vacuo*. Column chromatographic separation of the mixture thus obtained on silica using hexane–ethyl acetate (95:5) gave 1-cyclohexyl-1-octyn-3-ol as an oil (0.80 g, 10% yield): IR (film) 3607, 3467, 2238 cm^{-1}; ^1H NMR 0.89 (t, 3H, J = 6.7 Hz), 1.23–1.81 (m, 18H), 2.36 (m, 1H), 4.35 (m, 1H). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.88; H, 11.80.

Activated manganese dioxide (5.54 g) was added to a solution of the above acetylene (0.800 g, 3.85 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 24 h. The mixture was filtered, and the solvent was removed *in vacuo*. Purification of the mixture by column chromatography on silica gel using hexane–ethyl acetate (98:2) gave compound **1h** as an oil (0.500 g, 63% yield): IR (film) 2209, 1675 cm^{-1}; ^1H NMR δ 0.91 (t, 3H, J = 6.7 Hz), 1.26–1.85 (m, 16H), 2.53 (t superimposed on m, 3H, J = 7.5 Hz); HRMS calcd for $C_{14}H_{22}O$ 206.1671, found 206.1673. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.74. Found: C, 81.05; H, 10.76.

Reaction of *syn*-Benzaldoxime with α,β-Acetylenic Carbonyl Compounds. Synthesis of β-Dicarbonyl Compounds. A. Dioxane-DMF Solution. A solution of *syn*-benzaldoxime (0.133 g, 1.1 mmol) in dry DMF (8 mL) was added to a stirred suspension of sodium hydride (60% in mineral oil, 0.044 g, 1.1 mmol) in dry dioxane (8 mL) in an argon atmosphere at room temperature. After 0.5 h, a solution of the acetylenic carbonyl compound (1.0 mmol) in dry DMF (8 mL) was added, and the solution was stirred for 0.5 h. The dioxane was removed *in vacuo*, water was added to the residue, and the product was extracted into ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The crude β-dicarbonyl compound was then purified by the method indicated in Table 1.

B. DMSO. The reaction was carried out in exactly the same manner as described in method A except that DMSO was used as the solvent (total volume = 24 mL).

C. THF. Dimethyl 2-Oxosuccinate (7d). A solution of *syn*-benzaldoxime (0.187 g, 1.54 mmol) in dry THF (50 mL) was added to a stirred suspension of sodium hydride (60% in mineral oil; 0.062 g, 1.54 mmol) in dry THF (10 mL) in an argon atmosphere at room temperature. After 0.5 h, the solution was cooled to −20 °C, and a solution of dimethyl acetylenedicarboxylate (0.200 g, 1.40 mmol) in dry THF (20 mL) was added slowly. Stirring at −20 °C was continued for 2 h, and then saturated aqueous citric acid (5 mL) and water (50 mL) were added. The product was extracted into ethyl acetate, and the extract was dried over sodium sulfate and evaporated *in vacuo*. The crude product was purified in the manner indicated in Table 1. Benzonitrile, identified by its IR and ^1H NMR spectra, could be isolated in 57% yield by elution of the silica gel column with hexane–ether (85:15).

Methyl 3-nitrobenzoylacetate (7b): mp 69–70 °C (hexane–ether); IR ($CHCl_3$) 1746, 1700, 1655, 1631, 1537, 1392 cm^{-1}; the ^1H NMR spectrum shows that this compound exists as a 1:1 mixture of keto and enol forms ($CDCl_3$) δ 3.80 (s), 3.96 (s), 4.09 (s), 5.80 (s), 7.65 (t, J = 8.0 Hz), 7.74 (t, J = 8.0 Hz), 8.12 (d, J = 8.0 Hz), 8.33 (m), 8.48 (d, J = 8.0 Hz), 8.64 (t, J = 2.0 Hz), 8.79 (t, J = 2.0 Hz). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.03; N, 6.27. Found: C, 53.83; H, 4.07; N, 6.13.

1-Cyclohexyloctane-1,3-dione (7h). Oil: IR ($CHCl_3$) 1711, 1612 cm^{-1}; the ^1H NMR spectrum shows that this compound exists as an 8:1 mixture of enol and keto forms ($CDCl_3$) δ 0.88 (t, 3H, J = 6.6 Hz), 1.21–1.39 (m, 10H), 1.56–1.87 (m, 6H), 2.15 (m), 2.27 (t, J = 7.6 Hz), 2.50 (t, J = 7.6 Hz), 2.60 (t, J = 7.6 Hz), 3.58 (s), 5.46 (s); MS m/e (rel intensity) 224 (9), 168 (31), 153 (23), 141 (100), 111 (27), 83 (19); HRMS calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1780.

Synthesis of Methyl 2-Benzoyl-3-phenylpropionate (8). The sodium enolate **5a** was generated as in method A above on a 1 mmol scale. Benzyl bromide (0.188 g, 1.1 mmol) was added, and the solution was stirred at room temperature for 1 h. The reaction was then worked up as described above, and the product, purified as described in Table 1, was obtained as an oil (85% yield): IR ($CHCl_3$) 1740, 1688 cm^{-1}; ^1H NMR δ 3.35 (d, 2H, J = 7.3 Hz) 3.65 (s, 3H), 4.67 (t, 1H, J = 7.3 Hz), 7.23 (m), 7.39–7.62 (m), 7.96 (m). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.83; H, 6.10.

Synthesis of the *syn*-Benzaldoxime–Methyl Propiolate Adduct 10. A solution of the oximate anion (3.81 mmol) in THF (60 mL) was prepared as described in method C. A solution of methyl propiolate (0.250 g, 3.47 mmol) in dry THF (50 mL) was added slowly at room temperature. Stirring was continued for a further 0.5 h, and then the reaction was quenched with water and worked up as described in method C. The crude product was purified as indicated in Table 1. After crystallization from hexane, compound **10** (35% yield) had mp 34–36 °C: IR (film) 1715, 1635, 1613, 950 cm^{-1}; ^1H NMR δ 3.74 (s, 3H), 5.68 (d, 1H, J = 12.58 Hz), 7.46 (m, 3H), 7.66 (m, 2H), 8.03 (d, 1H, J = 12.58 Hz), 8.30 (s, 1H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.83. Found: C, 64.53; H, 5.52; N, 6.80.

Generation of the Enolate of Ethyl Formylacetate (11) and Alkylation with Benzyl Bromide. To a suspension of sodium hydride (0.021 g, 60% in mineral oil, 0.525 mmol) in dry DMF (15 mL) was added compound **10** (0.100 g, 0.487 mmol) with stirring at room temperature in an argon atmosphere. After 0.5 h, benzyl bromide (0.075 g, 0.438 mmol) was added, and stirring was continued for 1 h. Water was added to the solution, the products were extracted into ethyl acetate, and the extract was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified as indicated in Table 1. A 4:1 mixture of **12** and **13** was obtained as an oil (60% yield): IR (film) 1711, 1645, 1625 cm^{-1}; ^1H NMR δ 3.64 (s, **13**), 3.66 (s, **13**), 3.71 (s), 4.91 (s), 5.06 (s, **13**), 5.33 (d, J = 13.0 Hz), 7.24–7.48 (m), 7.55 (s, **13**), 7.70 (d, J = 13.0 Hz). This mixture was not separable by the usual chromatographic techniques.

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