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DMAP catalyzed reaction of β-ketoesters and dimethyl acetylenedicarboxylate: efficient synthesis of polysubstituted benzenes and biaryls

Vijay Nair,[a,*] N. Vidya,[a] A. T. Biju,[a] Ani Deepthi,[a] K. G. Abhilash[a] and Eringathodi Suresh[b]

[a]*Organic Chemistry Section, Regional Research Laboratory (CSIR), Trivandrum 695 019, Kerala, India*
[b]*Central Salt and Marine Chemicals Research Institute (CSIR), Bhavnagar 364 002, India*

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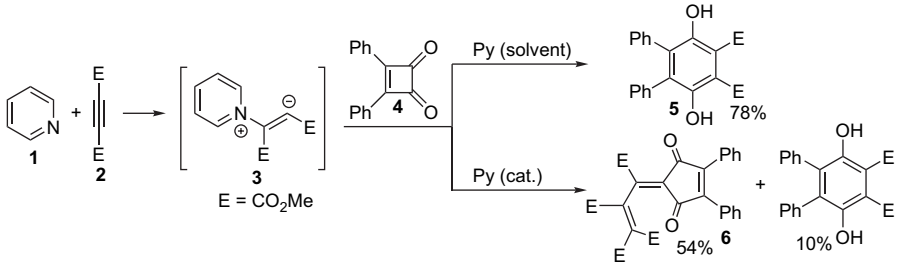
Abstract—A DMAP catalyzed tandem addition–cyclization–dehydration sequence involving dimethyl acetylenedicarboxylate and β-ketoesters leading to polysubstituted benzene/biaryl derivatives is presented.

1. Introduction

Benzene derivatives are uniquely important in organic chemistry. Not surprisingly therefore, the quest to develop efficient and versatile methods for the synthesis of substituted benzenes[1,2] has been a perennial theme in organic synthesis. The venerable Friedel–Crafts reaction[3] and the ortho-metallation strategy[4] can be used for introducing substituents into the benzene ring. The Reppe reaction,[5] the Vollhardt protocol,[6] the Diels–Alder strategy, and the Bergman cyclization[7] hold much promise for the synthesis of substituted benzenes. Biaryls are important as they constitute the core unit in many of the natural and synthetic compounds endowed with useful biological properties.[8] They are also useful as components in new organic materials like electroluminescent conjugated polymers,[9] semiconductors, and liquid crystals.[10] The Ullmann reaction,[11] the nucleophilic substitution reaction using organometallic aryls and activated arenes with electron withdrawing substituents,[12] the intramolecular transfer of aryl groups by a radical mechanism,[13] coupling reaction of various phenolic and non-phenolic aromatics by oxidation with di-*tert*-butyl peroxide (DTBP) or LTA[14] and nucleophilic addition of aryl organometallics to arynes[15] are good routes to biaryls.

In the course of our recent studies on the chemistry of zwitterionic species,[16] it was shown that interception of the zwitterion **3** with cyclobutene-1,2-diones provided selective access to either cyclopentenedione derivatives or hexa substituted benzene derivatives[17] depending on the amount of pyridine used (Scheme 1).

In the context of this interesting observation, it was surmised that the tandem addition of an enolate, generated from β-ketoesters by pyridine, to two molecules of acetylenic ester, if experimentally feasible, would generate a species, which



Scheme 1. Pyridine catalyzed reaction of DMAD with cyclobutene-1,2-diones.

Keywords: β-Ketoesters; DMAD; DMAP; Biaryl.
* Corresponding author. Tel.: +91 471 2490406; fax: +91 471 2491712; e-mail: vijaynair_2001@yahoo.com

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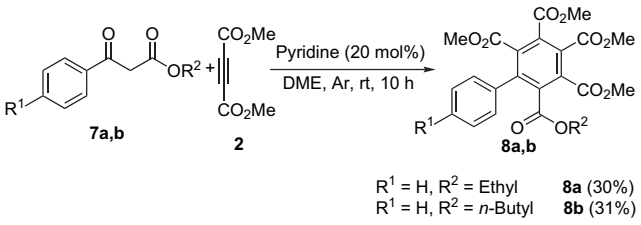
can transform into a hexatriene system well-disposed to undergo electrocyclization to afford a dihydrobenzene derivative, and the latter would undergo dehydration to deliver polysubstituted benzenes. The results of our studies validating the concept outlined above, leading to an unprecedented biaryl synthesis form the subject of this paper.

2. Results and discussion

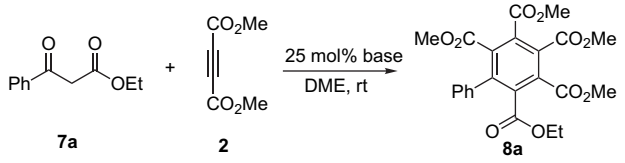
In the first instance, a solution of ethyl benzoyl acetate **7a** and dimethyl acetylenedicarboxylate (DMAD) **2** in DME was treated with 20 mol % pyridine at room temperature. The reaction afforded the fully substituted benzene derivative **8a** albeit in 30% yield (Scheme 2).



Scheme 2. Pyridine catalyzed reaction of DMAD with β-ketoesters.

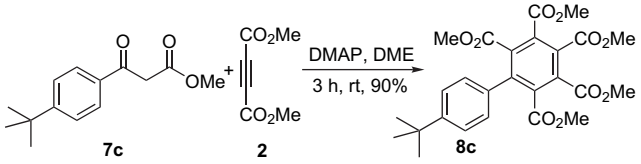
The enolate formation and subsequent annulation were investigated with different bases, and dimethyl aminopyridine (DMAP) was found to be the best catalyst for the transformation to biaryls; DABCO also gives comparable results, as summarized in Table 1.

Table 1. Optimization of reaction conditions



Entry	Base	Time (h)	DMAD (equiv)	Yield (%)
1	Pyridine	12	1	23
2	Pyridine	12	2.5	30
3	DABCO	3	2.5	90
4	DMAP	3	2.5	93
5	PPh_3	12	2.5	0
6	DBU	12	2.5	0
7	NaOMe	12	2.5	<10
8	NaH	12	2.5	<10

An illustrative example is the reaction of methyl-4-*tert*-butyl benzoyl acetate **7c** and DMAD in dry DME with 25 mol % of DMAP at room temperature under an argon atmosphere for 3 h affording the biphenyl derivative **8c** as a colorless crystalline solid in 90% yield (Scheme 3).



Scheme 3. DMAP catalyzed reaction of DMAD with β-ketoesters.

The product was characterized on the basis of spectroscopic data. In the IR spectrum, the ester carbonyl appeared at 1745 cm^{-1}. In the ^1H NMR spectrum, the carbomethoxy protons resonated at δ 3.89, 3.86, and 3.48. The ester carbonyls were discernible at δ 166.6, 166.0, and 165.5 in the ^{13}C NMR spectrum. Finally, the structure was unequivocally established by single crystal X-ray analysis (Fig. 1).[18]

The reaction was found to be general with various substituted β-ketoesters giving the substituted biaryls in excellent yields. The results are summarized in Table 2.

Mechanistically, the reaction can be interpreted as follows. The enolate generated by the deprotonation of β-ketoester adds to two molecules of DMAD in tandem, to furnish the

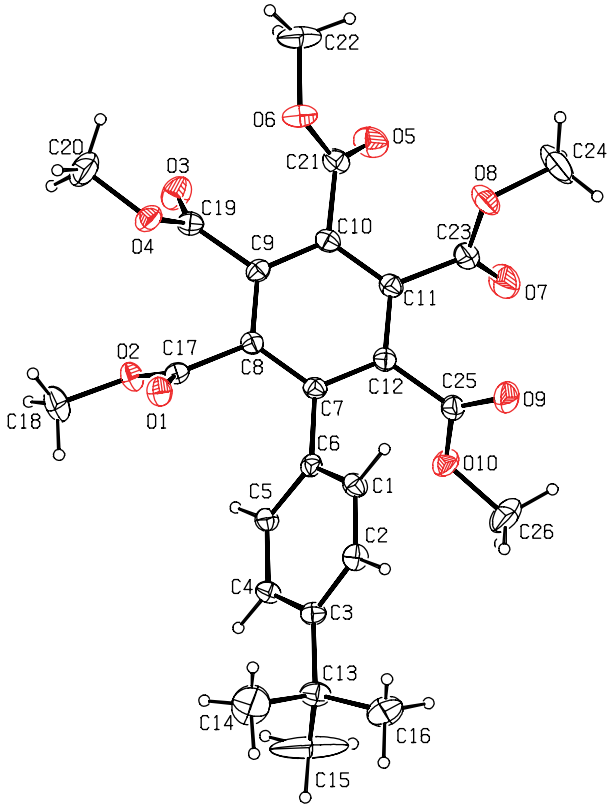
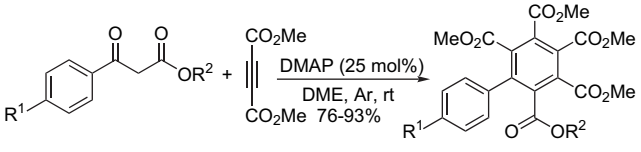
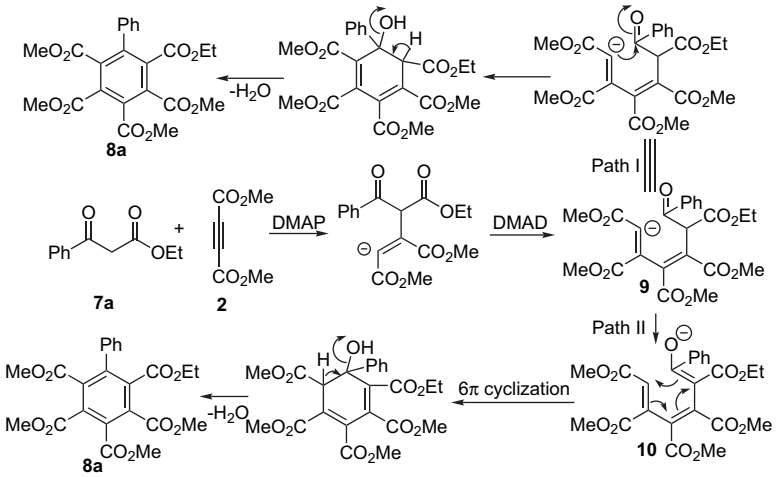


Figure 1. Single crystal X-ray structure of **8c**.

Table 2. DMAP catalyzed reaction of DMAD with various β-ketoesters



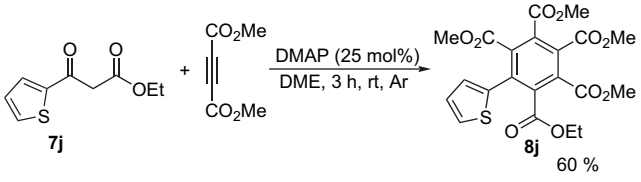
Entry	R^1	R^2	Product	Yield (%)
1	H	Ethyl	**8a**	93
2	H	*n*-Butyl	**8b**	86
3	Br	Methyl	**8d**	91
4	Br	*n*-Butyl	**8e**	85
5	F	*n*-Butyl	**8f**	86
6	F	Methyl	**8g**	88
7	CN	Methyl	**8h**	76
8	Ph	Methyl	**8i**	81



Scheme 4. Mechanistic rationalization.

vinyl anion **9**. Conceivably, this intermediate can transform into the product via two pathways. In path I, **9** undergo intramolecular addition of the vinylic anion to the benzoyl carbonyl followed by dehydration to afford **8a**. In pathway II, the enolate **10** generated from **9** by 1,5-proton transfer can undergo 6π-electrocyclization followed by dehydration to deliver **8a** (Scheme 4).

Thienyl substituted β-ketoester on treatment with DMAD in the presence of 25 mol % of DMAP also afforded the fully substituted benzene derivative in good yield (Scheme 5).



Scheme 5. Synthesis of fully substituted benzene derivative.

3. Conclusion

In conclusion, a new and an efficient protocol for the one pot synthesis of polysubstituted benzene/biaryl derivatives has been uncovered. The experimental simplicity and metal-free conditions of the synthesis are especially noteworthy.

4. Experimental

4.1. General

All reactions were conducted in oven-dried glassware sealed with rubber septa under a positive pressure of deoxygenated argon from a manifold. Solvents used for the experiments were distilled or dried as specified. Dimethyl acetylenedicarboxylate (DMAD), DMAP, and ethyl benzoyl acetate were purchased from Aldrich and used as received. The β-ketoesters used for our study are prepared from a known procedure.[19] All other reagents were purchased from local suppliers and used without purification. All reactions were monitored by TLC; visualization was effected with UV and/or by developing in iodine. Chromatography refers to open column chromatography on silica gel (100–200 mesh). Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Brücker DPX-300 MHz. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. IR spectra were recorded on Bomem MB series FT-IR spectrometer; absorbencies are reported in cm^{-1}. High-resolution mass spectra were obtained using Autospec M mass spectrometer. Elemental analyses were performed on a Perkin Elmer-2400 elemental analyzer.

4.2. General procedure for the synthesis of fully substituted benzene derivatives

To a stirred solution of β-ketoester (0.43 mmol) in anhydrous DME (10 mL) under an argon atmosphere was added DMAD (152 mg, 1.07 mmol) followed by DMAP (13 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, residue on silica gel column chromatography using 70:30 petroleum ether–ethyl acetate as eluent, to afford the respective product.

4.2.1. Compound 8a. Yield (221 mg, 93%). Colorless crystalline solid, mp 124–125 °C. IR (KBr) ν_{max}: 2955, 1738, 1571, 1443, 1412, 1328, 1251, 1219, 1096, 999 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.38–7.19 (m, 5H), 3.98–3.94 (m, 2H), 3.90 (s, 3H), 3.87 (s, 6H), 3.48 (s, 3H), 0.90 (uneven triplet, 3H, J_1=7.2 Hz, J_2=6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.8, 165.7, 165.3, 165.2, 140.3, 136.6, 136.4, 135.9, 132.1, 131.4, 131.1, 128.4, 128.2, 127.9, 127.6, 66.9, 64.4, 61.7, 53.4, 52.9, 52.3. HRMS (EI): *m/z* calcd for $C_{23}H_{22}O_{10}$: 458.1213, found: 458.1238.

4.2.2. Compound 8b. Yield (153 mg, 86%). Colorless crystalline solid, mp 106–107 °C. IR (KBr) ν_{max}: 2959, 1748, 1738, 1439, 1346, 1243, 1218, 1135, 1094, 996 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33–7.21 (m, 5H), 3.89 (s, 3H), 3.86 (s, 6H), 3.48 (s, 3H), 1.24 (uneven triplet, 2H, J_1= 5.7 Hz, J_2=6.9 Hz), 1.13–1.06 (m, 2H), 0.85–0.77 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 166.4, 166.1, 166.0, 165.5, 165.3, 140.3, 136.3, 136.6, 136.0, 132.2, 131.5, 130.2, 128.5, 128.3, 128.1, 65.6, 53.1, 52.6, 52.4, 51.8, 39.2, 30.3, 18.8. HRMS (EI): *m/z* calcd for $C_{25}H_{26}O_{10}$: 486.1526, found: 486.1468.

4.2.3. Compound 8c. Yield (192 mg, 90%). Colorless crystalline solid, mp 170 °C. IR (KBr) ν_{max}: 1745, 1610, 1568, 1512, 1442, 1352, 1251, 1182, 983 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.39 (d, 2H, J=5.4 Hz), 7.11 (d, 2H, J=8.4 Hz), 3.89 (s, 3H), 3.86 (s, 6H), 3.48 (s, 6H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 166.6, 166.0, 165.5, 151.6, 140.7, 136.8, 132.9, 131.3, 128.0, 125.1, 53.2, 53.1, 52.4, 34.7, 31.3. HRMS (FAB): *m/z* calcd (M^+) for $C_{26}H_{28}O_{10}$: 500.17, found: 500.36. The crystal structure for compound **8c** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 295899.

4.2.4. Compound 8d. Yield (184 mg, 91%). Colorless crystalline solid, mp 148–150 °C. IR (KBr) ν_{max}: 2953, 1742, 1732, 1542, 1440, 1221, 1001, 999 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H, J=8.4 Hz), 7.08 (d, 2H, J=8.1 Hz), 3.90 (s, 6H), 3.87 (s, 3H), 3.54 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.1, 165.8, 165.1, 139.2, 136.5, 134.7, 132.8, 131.4, 131.3, 130.0, 123.2, 53.3, 53.2, 52.7. Elemental analysis: Calcd for $C_{22}H_{19}BrO_{10}$, C, 50.50; H, 3.66. Found C, 50.82; H, 3.65.

4.2.5. Compound 8e. Yield (163 mg, 85%). Colorless crystalline solid, mp 123–125 °C. IR (KBr) ν_{max}: 2958, 1747, 1737, 1542, 1523, 1503, 1221, 1048, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H, J=8.4 Hz), 7.09 (d, 2H, J= 8.4 Hz), 3.92 (uneven triplet, 2H, J_1=6.6 Hz, J_2=9.0 Hz), 3.87 (s, 9H), 3.54 (s, 3H), 1.35–1.26 (m, 2H), 1.18–1.08 (m, 2H), 0.81 (uneven triplet, 3H, J_1=7.2 Hz, J_2=6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 166.1, 166.1, 165.8, 165.2, 139.0, 134.9, 131.4, 130.1, 123.2, 65.9, 53.2, 53.2, 53.1, 52.6, 30.1, 18.8. HRMS (FAB): For $C_{25}H_{25}BrO_{10}$: calcd ($M+Na^+$): 587.0529, found: 587.2785.

4.2.6. Compound 8f. Yield (190 mg, 86%). Colorless crystalline solid, mp 127–129 °C. IR (KBr) ν_{max}: 2958, 1747, 1732, 1537, 1513, 1455, 1216, 1102, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.23–7.18 (m, 2H), 7.11–7.05 (m, 2H), 3.92 (uneven triplet, 2H, J_1=6.9 Hz, J_2=6.6 Hz), 3.87 (s, 3H), 3.83 (s, 6H), 3.53 (s, 3H), 1.37–1.26 (m, 2H), 1.19–1.10 (m, 2H), 0.82 (uneven triplet, 3H, J_1=7.2 Hz, J_2=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.9, 165.2, 164.5, 161.2 (aromatic carbon attached to fluorine), 136.8, 132.9, 132.6, 131.8, 131.8, 131.4, 131.2, 115.9, 115.4, 107.6, 105.4, 65.8, 53.4, 53.2, 53.2, 53.1, 30.4, 30.2, 18.8. HRMS (FAB): *m/z* calcd for $C_{25}H_{25}FO_{10}$: (M^+): 504.1432, found: 504.3005.

4.2.7. Compound 8g. Yield (200 mg, 88%). Colorless crystalline solid, mp 136–138 °C. IR (KBr) ν_{max}: 2958, 1742, 1737, 1542, 1513, 1450, 1226, 1052, 980 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.21–7.05 (m, 4H), 3.90 (s, 3H), 3.87 (s, 6H), 3.53 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.8, 165.2, 164.4, 161.1 (aromatic carbon attached to fluorine), 139.3, 136.8, 132.6, 131.6, 131.3, 130.2, 115.5, 115.2, 53.2, 53.1, 52.6. HRMS (EI): *m/z* calcd for $C_{22}H_{19}FO_{10}$: 462.0962, found: 462.0965.

4.2.8. Compound 8h. Yield (174 mg, 76%). Colorless crystalline solid, mp 144–146 °C. IR (KBr) ν_{max}: 2229, 1736, 1606, 1504, 1444, 1352, 1328, 1236, 1180, 930 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, 2H, J=8.1 Hz), 7.34 (d, 2H, J=8.4 Hz), 3.91 (s, 3H), 3.88 (s, 6H), 3.54 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 165.5, 165.4, 164.7, 140.5, 138.5, 135.9, 131.7, 131.4, 131.4, 130.2, 129.2, 112.7, 53.6, 53.2, 53.1. HRMS (EI): *m/z* calcd for $C_{23}H_{19}NO_{10}$: 469.1009, found: 469.1043.

4.2.9. Compound 8i. Yield (165 mg, 81%). Colorless crystalline solid, mp 184–186 °C. IR (KBr) ν_{max}: 1739, 1606, 1442, 1330, 1255, 1220, 1184, 983 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.65–7.61 (m, 4H), 7.45 (uneven triplet, 2H, J_1= 7.08 Hz, J_2=7.62 Hz), 7.43 (d, 2H, J=8.0 Hz), 7.34 (d, 1H, J=7.2 Hz), 3.86 (s, 9H), 3.52 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.5, 166.0, 165.4, 141.3, 140.3, 140.1, 136.7, 134.8, 132.4, 131.5, 130.2, 128.9, 128.0, 127.8, 126.8, 53.3, 53.2, 52.9. HRMS (EI): *m/z* calcd for $C_{28}H_{24}O_{10}$: 520.1369, found: 520.1105.

4.2.10. Compound 8j. Yield (143 mg, 60%). Colorless crystalline solid, mp 113–115 °C. IR (KBr) ν_{max}: 1739, 1722, 1571, 1448, 1359, 1321, 1259, 1180, 900 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, 1H, J=5.1 Hz), 7.06–7.01 (m, 2H), 4.06 (q, 2H, J_1=J_2=7.2 Hz), 3.89 (s, 3H), 3.87 (s, 6H), 3.51 (s, 3H), 1.05 (uneven triplet, 3H, J_1=6.9 Hz, J_2=7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.7, 165.6, 165.1, 165.1, 137.7, 131.1, 129.1, 127.6, 127.01, 62.0, 53.2, 53.2, 53.1, 52.7, 13.6. HRMS (EI): *m/z* calcd for $C_{21}H_{20}O_{10}S$: 464.0777, found: 464.0790.

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