An Efficient Multicomponent Synthesis of Highly Functionalized Cyclopentenes

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Abstract: An efficient, one-pot and multicomponent synthesis of dialkyl 5,5-dicyano-3-aryl-2-cyclopentene-1,2-dicarboxylates is described. A mixture of a phenacyl bromide, malononitrile, and a dialkyl acetylenedicarboxylate in the presence of triphenylphosphine and triethylamine undergo a smooth addition reaction in absolute ethanol at ambient temperature to afford the highly functionalized cyclopentenes in good to excellent yields.

Key words: phenacyl bromides, alkynes, cyclopentenes, multicomponent reactions, cyclizations, intramolecular Wittig reactions

Recently multicomponent reactions (MCRs) in which three or more reactants are combined in a one-pot procedure have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound.[1] Thus, they are perfectly amenable to automation for combinatorial synthesis.[2] The immense possibilities of synthetic variations make it likely to find starting materials and conditions suitable for the discovery of new MCRs.[3]

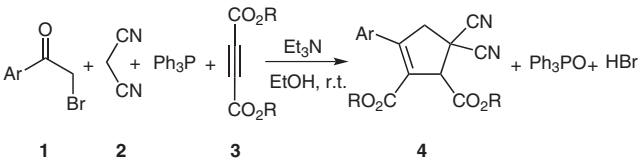
Five-membered carbocycles have received considerable attention because of their chemical and biological importance.[4] Among this family of compounds, cyclopentenes are particularly important intermediates in organic synthesis. Cyclopentenes are common substructures in a wide array of natural products and biologically active compounds.[4–6]

There have been many reports in the literature for the preparation of cyclopentene derivatives in the past few years. The most common synthetic approaches to cyclopentene derivatives involve: (*i*) classical intramolecular Michael-type conjugate addition to activated alkenes, alkynes,[7] and allenyl sulfones,[8] (*ii*) Ramberg–Bäcklund rearrangement of thiosugar-derived sulfones,[9] (*iii*) rearrangement of vinylcyclopropanes,[10] (*iv*) intramolecular Morita–Baylis–Hillman reaction,[11] (*v*) intramolecular ring-closing metathesis reaction,[12] and intramolecular Wittig reaction.[13]

In 2002, synthesis of a spirocyclopentene derivative was reported in which reaction between a dimedone derivative and dimethyl acetylenedicarboxylate in the presence of triphenylphosphine resulted to dimethyl 8,8-dimethyl-6,10-dioxo-3-phyenylspiro[4.5]deca-2-ene-1,2-dicarboxylate in fairly good yield.[14]

The intramolecular Wittig reaction, in which a C=C bond is formed by condensation of a carbonyl function with an alkylidenephosphorane group incorporated in the same molecule, has been applied to the preparation of common five-, six-, and also seven-membered carbo- and heterocycles and has been used as a key step in several routes to the synthesis of natural products.[13,15]

As part of our current studies on the development of efficient methods for the preparation of important carbo- and heterocyclic compounds,[16] herein we describe a one-pot multicomponent synthesis of highly functionalized cyclopentenes. Thus a mixture of a phenacyl bromide (**1**), malononitrile (**2**), triphenylphosphine, and a dialkyl acetylenedicarboxylate **3** in the presence of Et_3N undergo a new MCR at ambient temperature in absolute ethanol to afford dialkyl 5,5-dicyano-3-aryl-2-cyclopentene-1,2-dicarboxylates **4a–k** in 85–96% yields (Scheme 1, Table 1). All the reactions went to completion within a few hours. ^{1}H NMR spectroscopic analysis of the reaction mixtures clearly indicated formation of the corresponding 5,5-dicyano-3-aryl-2-cyclopentene-1,2-dicarboxylate **4** in good to excellent yields.[17]



Scheme 1

The structures of the isolated products **4** were deduced on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of **4a** showed absorptions at 2251, 1752 and 1724 cm^{-1} indicating the presence of nitrile and ester functionalities. The mass spectrum of **4a** displayed the molecular ion [M$^+$] peak at *m/z* = 310, which was consistent with the 1:1:1 ad-

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Table 1 Synthesis of Substituted Cyclopentenes **4a–k**

4	Ar	R	Yield (%)[a]
4a	Ph	Me	95
4b	4-$MeOC_6H_4$	Me	92
4c	4-ClC_6H_4	Me	88
4d	4-PhC_6H_4	Me	90
4e	4-MeC_6H_4	Me	96
4f	Ph	Et	85
4g	4-$MeOC_6H_4$	Et	93
4h	4-ClC_6H_4	Et	86
4i	4-MeC_6H_4	Et	90
4j	Ph	^{t}Bu	93
4k	4-ClC_6H_4	^{t}Bu	89

[a] Isolated yield.

duct of 2-bromo-1-phenylethanone, malononitrile, and dimethyl acetylenedicarboxylate losing a hydrogen bromide molecule and an oxygen atom. The ^{1}H NMR spectrum of **4a** showed two single sharp lines readily recognized as arising from the two methoxy (δ = 3.68 and 3.90 ppm) groups. One of the two diastereotopic H atoms of the cyclopentene methylene group was observed as a doublet (δ_A = 3.61 ppm, ^2J = 17.3 Hz) and the other one as a doublet of doublet (δ = 3.85 ppm, ^2J = 17.3, ^4J = 1.6 Hz) as a result of a further long range coupling with the ring methine proton. The ring methine proton was seen as a fairly broad singlet (δ = 4.61 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed characteristic signals at δ = 34.50 [due to the $C(CN)_2$], 49.50 (arising from the CH_2), 52.16, 53.59 (for the two OCH_3), and 60.92 ppm (due to the $CHCO_2CH_3$) in the aliphatic region of the spectrum. Four characteristic resonances were evident at δ = 113.21, 115.27 (for the two CN groups), 162.85 and 167.64 ppm(due to the two carbonyl groups) along with other three CH and three quaternary carbons in the downfield region of the spectrum in agreement with the proposed structure.[17]

A mechanistic rationalization for this reaction is provided in Scheme 2. Initially, treatment of phenacyl bromide with malononitrile in the presence of Et_3N produces 2-(2-aryl-2-oxoethyl)malononitrile **5**. Next, the reactive 1:1 zwitterionic intermediate **6**, formed from the initial addition of triphenylphosphine to the electron-deficient acetylenic compound **3** , s protonated by the in situ prepared CH-acid **5**. Then, the positively charged vinyl phosphonium ion **8** may be attacked by the conjugate base of the acid **7** to form phosphorane **9**. This adduct may undergo intramolecular Wittig reaction of the ylide moiety with the adjacent ketone carbonyl to afford the isolated 5,5-dicyano-3-aryl-2-cyclopentene-1,2-dicarboxylate **4** by removal of triphenylphosphine oxide.

In conclusion, we have succeeded in synthesizing dialkyl 5,5-dicyano-3-aryl-2-cyclopentene-1,2-dicarboxylates of potential synthetic interest via a one-pot and multicomponent reaction between phenacyl bromides, malononitrile, and dialkyl acetylendicarboxylates in the presence of triphenylphosphine. Use of simple and readily available starting materials, mild reaction conditions, relatively short reaction times, and high yields of the products are the main advantages of this reaction. The simplicity of the present procedure makes it an interesting alternative to other approaches. In view of extensive use of cyclopentenes as synthetic intermediates and target compounds, the dialkyl 5,5-dicyano-3-aryl-2-cyclopentene-1,2-dicarboxylates prepared in the present study may find useful applications in synthetic organic chemistry.

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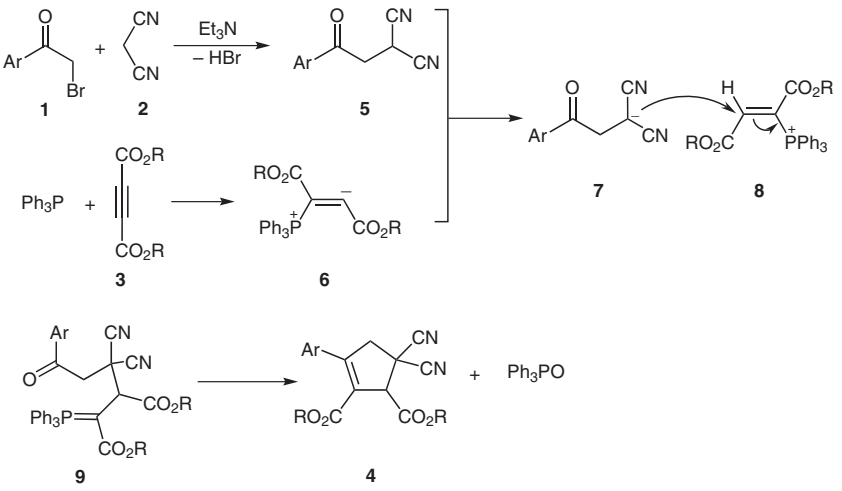

Scheme 2

References and Notes

(1) (a) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (b) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575. (c) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

(2) (a) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

(3) (a) Weber, L. *Curr. Opin. Chem. Biol.* **2000**, *4*, 295. (b) Dömling, A. *Curr. Opin. Biol. Chem.* **2000**, *4*, 318.

(4) (a) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477; and previous reviews in this series. (b) *Prostaglandins: Prostaglandins, Leukotrienes and Essential Fatty Acids*; Horrobin, D. F.; Manku, M. S.; Sirois, P.; Borgeat, P., Eds.; Churchill Livingston: Edinburgh, **2002**. (c) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Curti, C. *Stud. Nat. Prod. Chem.* **2003**, *29*, 449.

(5) (a) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (b) Hudlicky, T.; Kutchan, T. M.; Neqvi, S. M. *Org. React.* **1985**, *33*, 247.

(6) Kim, K. H.; Miller, M. J. *Tetrahedron Lett.* **2003**, *44*, 4571.

(7) (a) Winterfeldt, E. *Kontakte (Darmstadt)* **1987**, 37; *Chem. Abstr.* **1988**, *109*, 22316d. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Vol. 9; Tetrahedron Organic Chemistry Series, Pergamon: Oxford, **1992**. (c) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.

(8) Mukai, C.; Ukon, R.; Kuroda, N. *Tetrahedron Lett.* **2003**, *44*, 1583.

(9) McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 1197; and references therein.

(10) (a) Mil'vitskaya, A. M.; Tarakanova, A. V.; Plate, A. F. *Russ. Chem. Rev.* **1976**, *45*, 469. (b) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (c) Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545. (d) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **1999**, *64*, 3567.

(11) (a) Jellerichs, B. G.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758. (b) Krafft, M. E.; Haxell, T. F. N. *J. Am. Chem. Soc.* **2005**, *127*, 10168. (c) Krafft, M. E.; Seibert, K. A. *Synlett* **2006**, 3334.

(12) (a) Schmidt, B.; Pohler, M. *Org. Biomol. Chem.* **2003**, *1*, 2512. (b) Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405; and references cited therein.

(13) (a) Bercker, K. *Tetrahedron* **1979**, *36*, 1717; and references cited therein. (b) Nagao, T.; Suenaga, T.; Ichihashi, T.; Fujimato, T.; Yamamoto, I.; Kakehi, A.; Iriye, R. *J. Org. Chem.* **2001**, *66*, 890. (c) Majik, M. S.; Parameswaran, P. S.; Tilve, S. G. *Helv. Chim. Acta* **2008**, *91*, 1500.

(14) Ramazani, A.; Fotouhi-Ardakani, E. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002**, *41*, 596.

(15) (a) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recl.* **1997**, 1283; and references cited therein. (b) Kumar, P.; Saravanan, K. *Tetrahedron* **1998**, *54*, 2161. (c) Azizian, J.; Karimi, A. R.; Soleimani, E.; Mohammadi, A. A.; Mohammadzadeh, M. R. *Hetroat. Chem.* **2008**, *17*, 277. (d) Kumar, P.; Bodas, M. *Org. Lett.* **2000**, *2*, 3821. (e) Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2001**, *3*, 2875. (f) Arndtsen, B. A.; Lu, Y. *Org. Lett.* **2009**, *11*, 1369.

(16) (a) Adib, M.; Ansari, S.; Feizi, S.; Bijanzadeh, H. R. *Synlett* **2010**, 921. (b) Adib, M.; Mohammadi, B.; Ansari, S.; Bijanzadeh, H. R.; Zhu, L. G. *Synthesis* **2010**, 1526. (c) Adib, M.; Ansari, S.; Fatemi, S.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2010**, *66*, 2723. (d) Adib, M.; Ansari, S.; Mohammadi, A.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2010**, *51*, 30. (e) Adib, M.; Ansari, S.; Feizi, S.; Asgarian Damavandi, J.; Mirzaei, P. *Synlett* **2009**, 3263. (f) Adib, M.; Mahdavi, M.; Ansari, S.; Malihi, F.; Zhu, L. G.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2009**, *50*, 7246. (g) Adib, M.; Sheibani, E.; Bijanzadeh, H. R.; Zhu, L. G. *Tetrahedron* **2008**, *64*, 10681. (h) Adib, M.; Mohammadi, B.; Bijanzadeh, H. R. *Synlett* **2008**, 3180. (i) Adib, M.; Mohammadi, B.; Bijanzadeh, H. R. *Synlett* **2008**, 177. (j) Adib, M.; Mohammadi, B.; Mahdavi, M.; Abbasi, A.; Riazati Kesheh, M. *Synlett* **2007**, 2497.

(17) **General Procedure for the Preparation of Compounds 4a–k**

A solution of the appropriate phenacyl bromide (1 mmol), malononitrile (1 mmol), and Et_3N (1 mmol) in EtOH (3 mL) was stirred at ambient temperature for 1 h. After addition of Ph_3P (1 mmol), a solution of the appropriate dialkyl acetylenedicarboxylate (1 mmol) in EtOH (2 mL) was dropwise added to the reaction mixture over 25 min, which then was stirred at ambient temperature for 5 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (Merck silica gel 230–240 mesh) using *n*-hexane–EtOAc (3:1) as eluent. The solvent was removed and the product was obtained.

Dimethyl 5,5-Dicyano-3-phenyl-2-cyclopentene-1,2-dicarboxylate (4a)

Colorless crystals; mp 130–131 °C. IR (KBr): 2251 (CN), 1752 and 1724 (C=O) cm^{-1}. MS (EI): *m/z* (%) = 310 (100) [M^+]. Anal. Calcd (%) for $C_{17}H_{14}N_2O_4$ (310.31): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.7; H, 4.6; N, 8.9. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.61 (d, ^2J = 17.3 Hz, 1 H, CH), 3.68 (s, 3 H, OCH_3), 3.85 (dd, ^2J = 17.3 Hz, ^4J = 1.6 Hz, 1 H, CH), 3.90 (s, 3 H, OCH_3), 4.61 (br s, 1 H, C*H*CO_2CH_3), 7.37–7.45 (m, 5 H, 5 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 34.50 [*C*$(CN)_2$], 49.50 (CH_2), 52.16 and 53.59 (2 × OCH_3), 60.92 (*C*HCO_2CH_3), 113.21 and 115.27 (2 × CN), 124.41 (C), 128.09, 128.38 and 130.17 (3 × CH), 132.39 and 151.84 (2 × C), 162.85 and 167.64 (2 × C=O).

Diethyl 3-(4-Chlorophenyl)-5,5-dicyano-2-cyclopentene-1,2-dicarboxylate (4h)

Colorless crystals; mp 97–99 °C. IR (KBr): 2255 (CN), 1735 and 1715 (shoulder; C=O) cm^{-1}. MS (EI): *m/z* (%) = 374 (30) [M^+ ^{37}Cl], 372 (100) [M^+ ^{35}Cl]. Anal. Calcd (%) for $C_{19}H_{17}ClN_2O_4$ (372.81): C, 61.21; H, 4.60; N, 7.51. Found: C, 61.2; H, 4.6; N, 7.4. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.37 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 3.57 (d, ^2J = 17.3 Hz, 1 H, CH), 3.80 (dd, ^2J = 17.3 Hz, ^4J = 1.5 Hz, 1 H, CH), 4.12 and 4.17 [2 × dq, *AB*X_3 system, ^2J = 11.0 Hz, ^3J = 7.1 Hz, 2 H, $OCH_AH_BCH_3$], 4.31 and 4.36 [2 × dq, *AB*X_3 system, ^2J = 10.7 Hz, ^3J = 7.2 Hz, 2 H, $OCH_AH_BCH_3$], 4.56 (s, 1 H, C*H*$CO_2C_2H_5$), 7.35 (d, *J* = 8.7 Hz, 2 H, 2 × CH), 7.38 (d, *J* = 8.7 Hz, 2 H, 2 × CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.83 and 14.07 (2 × OCH_2CH_3), 34.44 [*C*$(CN)_2$], 49.32 (CH_2), 60.74 (*C*H$CO_2C_2H_5$), 61.50 and 63.5 (2 × OCH_2CH_3), 113.06 and 115.27 (2 × CN), 125.61 (C), 128.59 and 129.61 (2 × CH), 130.85, 136.16 and 150.14 (3 × C), 162.15 and 167.11 (2 × C=O).