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DABCO-Mediated Isocyanide-Based Multicomponent Reaction: Synthesis of Highly Substituted Cyclopentenes

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Li-Rong Wen,*[a] Ming-Chao Lan,[a] Wen-Kui Yuan,[a] and Ming Li*[a,b]

Highly substituted cyclopentenes can be accessed rapidly from isocyanides, aldehydes and malononitrile or ethyl cyanoacetate (AB_2C_2) by DABCO as a catalyst under solvent-free conditions at 40 °C within 30 min.

Introduction

Five-membered carbocycles as structural frameworks are often found in natural products and medicinally important agents,[1] such as *ent*-isodehydrocostus lactone, (+)-podoandin,[2] and potential anti-HIV agents[3] (Figure 1), Additionally, some can be used as potent potentiators of AMPA receptors,[4] COX-2 inhibitors,[5] nucleoside-type antibodies[6] and mannosidase inhibitors.[7] Due to the importance of cyclopentenes, remarkable progress has been made which led to the development of many innovative strategies, concepts and methodologies.[8] Among the known synthetic methods, phosphine-catalyzed [3+2] cycloaddition, developed by Lu in 1995,[9] is considered to be a powerful synthetic approach. Although a variety of methodologies and protocols have been reported by a number of organic or pharmaceutical chemists,[10] it is of great importance to explore a novel and efficient synthetic method to meet increasing scientific and practical demands.

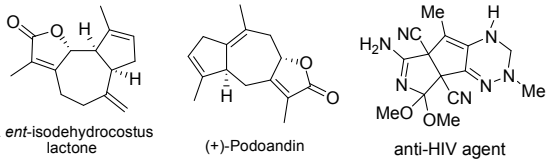
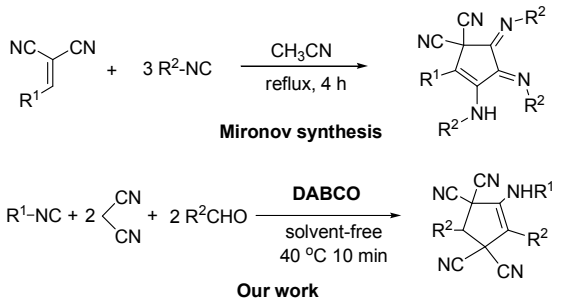


Figure 1. Selected examples for cyclopentene-containing natural products and medicinal agents.

Zwitterionic species are known to arise from the addition of nucleophiles such as triphenylphosphine,[11] pyridine,[12] quinoline,[13] as well as other nitrogen heterocycles[14] to the activated π systems. Isocyanides can also form zwitterions with suitable electrophilic unsaturated systems and develop novel protocols for the synthesis of heterocycles and carbocycles.[15] Mironov discovered a new reaction of substituted arylidenemalononitriles with three equiv. of isocyanides leading to the cyclopentene derivatives.[16] Based on our previous endeavors in exploring novel multicomponent reactions,[17] herein, we report a novel five-component reaction (AB_2C_2) of isocyanides, aldehydes, and malononitrile derivatives in 1:2:2 ratio to yield highly substituted cyclopentenes under solvent-free conditions by DABCO as the catalyst (Scheme 1).



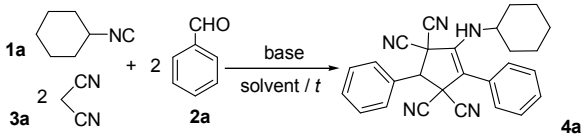
Scheme 1

Results and discussion

The reaction conditions were optimized by using cyclohexyl isocyanide **1a** (0.5 mmol), benzaldehyde **2a** (1.0 mmol) and malononitrile **3a** (1.0 mmol) as model substrates with various bases, solvents at different temperatures (Table 1). When the model reaction was stirred in CH_3CN at room temperature for 8 h or in refluxing THF for 4 h without addition of any base, only Mironov product[16] as a major was obtained and no target compound **4a** was observed (Table 1, entries 1–2). However, when DABCO (1.0 equiv) was added, a highly substituted cyclopentene **4a** was obtained in moderate yield of 46% (Table 1, entry 3). Then other bases, such as Et_3N, Ph_3P, and pyridine, were examined, and the results revealed that they all failed to effectively promote this reaction (Table 1, entries 4–6). Other solvents, such as THF, $(Et)_2O$, DCM, were next tested in the presence of DABCO (1.0 equiv) at room or reflux temperature to improve the yield of **4a**, but the results were all unsatisfactory (Table 1, entries 7–10). After much careful experimentation, and considering that the solvent-free reaction is an important synthetic procedure from the viewpoint of green chemistry,[18] the solvent-free conditions were attempted. To our delight, a break-through result was achieved, **4a** was obtained in

64% isolated yield within only 10 min at 40 ºC (Table 1, entry 12). Thus, the amount of DABCO were examined (Table 1, entries 14-17). The best result was obtained in the mole ratio 0.5:1.0:1.0 for **1a**/**2a**/**3a** using DABCO (0.5 equiv) as the base at 40 ºC under solvent-free conditions.

Table 1. Optimization of reaction conditions for **4a**.[a]



Entry	Solvent	Base (equiv)	Temp (ºC)	Time (h)	Yield[b] (%)
1	CH_3CN	—	r.t	8	0
2	THF	—	reflux	4	0
3	CH_3CN	DABCO (1.0)	r.t.	8	46
4	CH_3CN	Et_3N (1.0)	r.t.	8	26
5	CH_3CN	Ph_3P (1.0)	r.t.	8	21
6	CH_3CN	pyridine (1.0)	r.t.	8	24
7	THF	DABCO (1.0)	r.t.	8	26
8	$(Et)_2O$	DABCO (1.0)	r.t.	8	21
9	DCM	DABCO (1.0)	r.t.	8	16
10	CH_3CN	DABCO (1.0)	reflux	2	—[c]
11	—[d]	DABCO (1.0)	r.t.	10 min	42
12	—[d]	DABCO (1.0)	40	10 min	64
13	—[d]	DABCO (1.0)	60	10 min	62
14	—[d]	DABCO (0.75)	40	10 min	63
15	—[d]	**DABCO (0.5)**	**40**	**10 min**	**64**
16	—[d]	DABCO (0.25)	40	10 min	35
17	—[d]	DABCO (1.25)	40	10 min	64

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), base (equiv. based on **1a**), solvent (1 mL). [b] Isolated yields based on **1a**. [c] Complex mixture. [d] Solvent-free conditions.

With the optimized conditions in hand, the scope of the five-component reaction was studied, and the results are illustrated in Table 2.

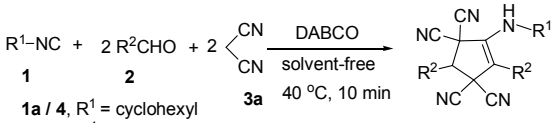
As can be seen from Table 2, various aromatic aldehydes **2** bearing both electron-donating and electron-withdrawing substituents at 2-, 3- or 4-position on the aromatic ring had proven to be reliable substrates for this five-component reaction with **1a** or **1b** and **3a**, providing the desired cyclopentenes **4**/**5** in good yields. Unfortunately, however, aliphatic aldehydes such as butyraldehyde failed to afford the desired products.

It is worthwhile to note that when an aryl isocyanide such as benzeneisocyanide was employed to react with benzaldehyde **2a** and malononitrile **3a** under the optimized conditions, the reaction system was complex and no target compound was observed.

The structures of the products **4**/**5** were identified by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data, and unequivocally confirmed by X-ray diffraction analysis of single crystal of **5e** (Figure S1 in SI).

Encouraged by these results, we further pursued the scope of the reactions with respect to the substrates **3**. Surprisingly, when ethyl cyanoacetate **3b** replaced **3a** to react with **1a** and **2a** under the above conditions, the reaction did not give rise to the tautomerization compound like compounds **4**/**5** directly**,** but a decarboxylation product **6a** was obtained. This observation was certified by ^{1}H NMR spectrum and the X-ray single crystal diffraction analysis of **6a** (Figure S2 in SI).

Table 2. Synthesis of **4/5** based on malononitrile **3a**.[a]

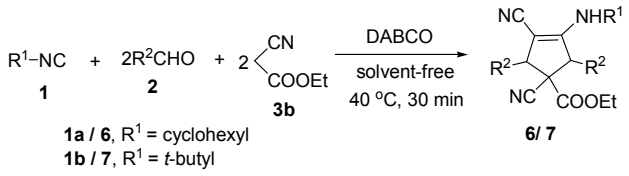


Entry	**1**	**2** / R^2	**4/5**	Yield[b] (%)
1	**1a**	**2a** C_6H_5	**4a**	64
2	**1a**	**2b** 4-ClC_6H_4	**4b**	68
3	**1a**	**2c** 4-BrC_6H_4	**4c**	68
4	**1a**	**2d** 4-FC_6H_4	**4d**	70
5	**1a**	**2e** 4-$CH_3C_6H_4$	**4e**	62
6	**1a**	**2f** 3-ClC_6H_4	**4f**	67
7	**1a**	**2g** 3-BrC_6H_4	**4g**	66
8	**1a**	**2h** 3-$CH_3OC_6H_4$	**4h**	58
9	**1a**	**2i** 3-$CH_3C_6H_4$	**4i**	60
10	**1a**	**2j** 2-ClC_6H_4	**4j**	63
11	**1a**	**2k** 2-BrC_6H_4	**4k**	63
12	**1a**	**2l** 2-FC_6H_4	**4l**	65
13	**1b**	**2a** C_6H_5	**5a**	64
14	**1b**	**2b** 4-ClC_6H_4	**5b**	62
15	**1b**	**2c** 4-BrC_6H_4	**5c**	62
16	**1b**	**2d** 4-FC_6H_4	**5d**	64
17	**1b**	**2e** 4-$CH_3C_6H_4$	**5e**	60
18	**1a**	**2m** *n*-Bu	**4m**	0

[a] Reaction conditions: isocyanides **1** (0.5 mmol), aldehydes **2** (1.0 mmol), malononitrile **3a** (1.0 mmol), DABCO (0.25 mmol), 40 °C, 10 min. [b] Isolated yields based on isocyanides.

The feasibility of employing other aromatic aldehydes to react with ethyl cyanoacetate (**3b**) and isocyanides were also investigated, the results demonstrated that all of the reactions proceeded smoothly (Table 3).

Table 3. Synthesis of **6/7** based on ethyl cyanoacetate **3b**.[a]

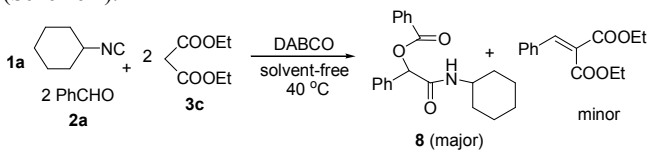


Entry	**1**	**2** / R^2	**6/7**	Yield[b] (%)
1	**1a**	**2a** C_6H_5	**6a**	57
2	**1a**	**2b** 4-ClC_6H_4	**6b**	64
3	**1a**	**2d** 4-FC_6H_4	**6c**	68
4	**1a**	**2i** 3-$CH_3C_6H_4$	**6d**	55
5	**1a**	**2l** 2-FC_6H_4	**6e**	60
6	**1b**	**2b** 4-ClC_6H	**7a**	57
7	**1b**	**2e** 4-$CH_3C_6H_4$	**7b**	54

[a] Reaction conditions: isocyanides **1** (0.5 mmol), aldehydes **2** (1.0 mmol), ethyl cyanoacetate **3b** (1.0 mmol), DABCO (0.25 mmol), 40 °C, 30 min. [b] Isolated yields based on isocyanides.

This observation motivated us to investigate diethyl malonate (**3c**) instead of **3a** and **3b** under the same conditions. Unfortunately, only a small amount of Passerini product **8** and the product from the

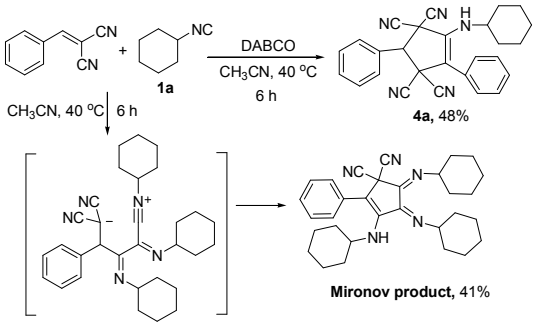
reaction of diethyl manoate (**3c**) with an aldehyde were observed (Scheme 2).



Scheme 2. The study on reaction of diethyl malonate **3c**.

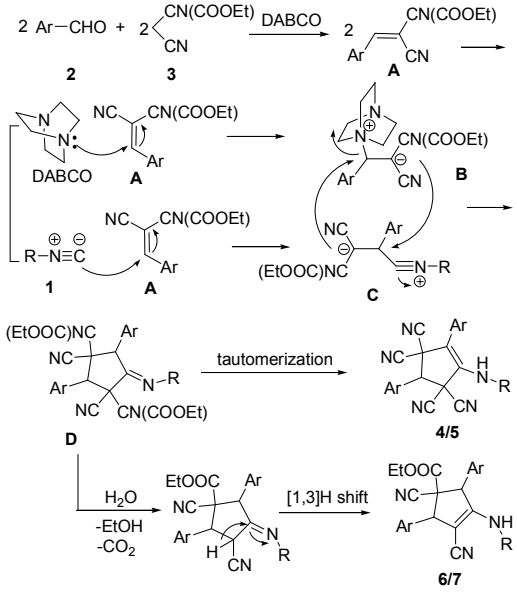
Next, we attempted the possibility of applying this reaction with two different aldehydes such as a bearing electron-withdrawing substituent aldehyde **2d** and a bearing electron-donating substituent aldehyde **2e**. When the ratio of **2d** and **2e** was 1:1, 36% cross-coupling product (**4de** or **4ed**) was obtained, while **4d** and **4e** were also produced in 27 and 24% yields, respectively (The yields were given by LC-MS based on the peak area. See Figure S3 in SI). As we can see from LC-MS, it is very hard to isolate the cross-coupling products, and therefore their structures were not ascertained.

To justify the role of DABCO, we performed the reaction by using directly 2-benzylidenemalononitrile (1 mmol) and cyclohexyl isocyanide **1a** (0.5 mmol) with 0.5 equiv of DABCO (0.25 mmol) in CH_3CN (0.5 mL) at 40 °C for 6 h; the result revealed only the desired product **4a** was obtained; whereas just the Mironov product[16] was provided without adding DABCO (Scheme 3). Undoubtedly, in this reaction process, the key step may be the formation of a zwitterion derived from DABCO with one 2-arylidenemalononitrile formed in situ from an aldehyde and a malononitrile, which were attacked by another highly reactive zwitterion generated in situ from an isocyanide and another 2-arylidenemalononitrile. We think that in situ generation of both of the reactive zwitterionic intermediates would be essential for the reaction.



Scheme 3. Exploitation for mechanism.

Although we have not experimentally established the mechanism of the reaction, a plausible mechanism is represented in Scheme 4 based on the above experimental results. First, aldehydes **2** react with malononitrile **3a** through Knoevenagel condensation to give the intermediate arylidenemalononitriles **A** by DABCO as the catalyst. Next, DABCO as a nucleophilic trigger reacts with **A** to generate a intermediate **B**, meanwhile, another **A** reacts with an isocyanide **1** to give a reactive zwitterionic intermediate **C**, then **B** and **C** undergo a [3+2] cyclization to give the intermediate **D** with the elimination of DABCO. The latter isomerizes to give the cyclopentenes **4**/**5**, or provides products **6**/**7** through losing a molecule of ethanol and decarboxylation followed by a [1,3]-H shift.



Scheme 4. Proposed mechanism for products **4**-**7**.

Conclusion

In conclusion, we have demonstrated a novel rapid and direct isocyanide-based five-component reaction for the synthesis of fully substituted cyclopentenes via DABCO-catalyzed annulations under solvent-free conditions within 30 min, The synthetic procedures have the advantages of mild reaction conditions, short reaction time, convenient handling as well as a wide substrate scope, which make this method useful for the synthesis of potentially biologically active cyclopentene derivatives.

Experimental

General Remarks. All reagents and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. Melting points were recorded on a RY-1 microscopic melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on 500 MHz and ^{13}C NMR spectra were recorded on 125 MHz by using a Bruker Avance 500 spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). IR spectra were recorded on a Nicolet iS10 FT-IR spectrometer and only major peaks are reported in cm^{-1}. Mass spectra were performed on an Ultima Global spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on Saturn 724+ instrument.

General procedure for the preparation of compounds 4–7. In a round bottom flask equipped with a magnetic bar, a mixture of isocyanides **1** (0.5 mmol, 1 equiv), aromatic aldehydes **2** (1.0 mmol, 2.0 equiv), and **3** (1.0 mmol, 2.0 equiv) was stirred at 40 °C with DABCO (0.25 mmol, 0.5 equiv) as the catalyst for a appropriate time. After completion of the

reaction as indicated by TLC (petroleum ether−EtOAc, 10:1, v/v), the crude product was purified by column chromatography (petroleum ether−EtOAc, 10:1, v/v) and afforded the pure products.

4-(Cyclohexylamino)-2,5-diphenylcyclopent-4-ene-1,1,3,3-tetracarbonitrile (4a). White powder; yield: 64%; mp 155–157 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.99–1.93 (m, 10H, CH_2), 3.06–3.08 (m, 1H, CH), 4.01 (d, J = 9.50 Hz, 1H, NH), 4.46 (s, 1H, CH), 7.47–7.78 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.6, 25.0, 33.7, 46.1, 48.1, 53.6, 58.6, 104.4, 110.7, 111.9, 112.1, 113.2, 128.6, 129.2, 129.4, 129.7, 129.8, 130.2, 131.4, 138.4; IR (KBr) v: 3365, 2925, 2852, 2250, 1663, 1517, 1501, 1457, 1098, 753, 702 cm^{-1}; HRMS (ESI-TOF$^+$): m/z calcd for $C_{27}H_{24}N_5$ [(M+H)$^+$], 418.2032; found, 418.2039.

4-(*tert*-Butylamino)-2,5-diphenylcyclopent-4-ene-1,1,3,3-tetracarbonitrile (5a). White powder; yield: 64%; mp 113–114 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (s, 9H, CH_3), 3.74 (s, 1H, NH), 4.43 (s, 1H, CH), 7.51–7.58 (m, 8H, ArH), 7.78 (d, J = 6.55 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 30.6, 47.8, 48.2, 55.7, 58.8, 111.1, 111.7, 112.6, 112.9, 114.4, 128.6, 129.2, 129.6, 129.7, 129.9, 130.4, 130.7, 131.5, 139.7; IR (KBr) v: 3382, 3063, 2973, 2932, 2873, 2248, 1655, 1575, 1500, 1475, 1198, 1114, 754, 700 cm^{-1}; HRMS (ESI-TOF$^+$): m/z calcd for $C_{25}H_{21}N_5Na$ [(M+Na)$^+$], 414.1689; found, 414.1690.

Ethyl 1,3-dicyano-4-(cyclohexylamino)-2,5-diphenylcyclopent-3-enecarboxylate (6a). White powder; yield: 57%; mp 134–136 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.64–0.67 (t, J = 7.15 Hz, 3H, CH_3), 1.09–2.37 (m, 10H, CH_2), 3.47–3.50 (m, 2H, CH_2), 4.11 (m, 1H, CH), 4.38 (d, J = 8.45 Hz, 1H, NH), 4.66 (s, 1H, CH), 4.90 (s, 1H, CH), 7.32–7.42 (m, 8H, ArH), 7.49 (d, J = 7.40 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.2, 24.0, 24.3, 25.4, 33.3, 33.6, 52.5, 57.7, 59.2, 60.0, 62.1, 69.9, 118.8, 118.9, 128.4, 128.6, 129.1, 129.4, 130.7, 131.1, 134.3, 156.0, 162.9; IR (KBr) v: 3317, 2934, 2856, 2247, 2183, 1748, 1607, 1581, 1537, 1495, 1454, 1222, 752, 703 cm^{-1}; HRMS (ESI-TOF$^+$): m/z calcd for $C_{28}H_{30}N_3O_2$ [(M+H)$^+$], 440.2338; found, 440.2345.

Ethyl 3-(*tert*-butylamino)-2,5-bis(4-chlorophenyl)-1,4-dicyanocyclopent-3- enecarboxylate (7a). White powder; yield: 57%; mp 154–156 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.71–0.74 (t, J = 7.18 Hz, 3H, CH_3), 1.52 (s, 9H, CH_3), 3.55–3.59 (m, 2H, CH_2), 4.48 (s, 1H, NH), 4.61 (s, 1H, CH), 4.88 (s, 1H, CH), 7.34–7.42 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.2, 29.7, 30.2, 30.5, 53.6, 58.0, 58.4, 60.8, 62.5, 70.1, 118.3, 120.3, 128.7, 129.4, 129.5, 130.5, 132.3, 132.8, 134.8, 136.0, 153.7, 162.8; IR (KBr) v: 3362, 2979, 2936, 2874, 2251, 2187, 1741, 1613, 1575, 1534, 1492, 1461, 1398, 1219, 819 cm^{-1}; HRMS (ESI-TOF$^+$): m/z calcd for $C_{26}H_{26}Cl_2N_3O_2$ [(M+H)$^+$], 482.1402; found, 482.1412.

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Notes and references

[a] *State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China*

[b] *State Key Laboratory of Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, P. R. China*

E-mail:liming928@qust.edu.cn; wenlirong@qust.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for all new compounds, and crystal data for **5e** and **6a** (CIFs). See DOI: 10.1039/c000000x/

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