Stereoselective Synthesis of Functionalized Cyclopropane Derivatives via α-Thiocyanate Ketone-Based Three-Component Reaction

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Received 30 March 2011; revised 19 May 2011

Abstract: α-Thiocyanate ketone-based three-component reactions have been established for the stereoselective synthesis of functionalized electron-deficient *trans*-cyclopropanes. The multicomponent reactions were conducted by reacting readily available and inexpensive starting materials under microwave irradiation. The procedures are very facile, highly stereoselective, and avoids the use of ylides.

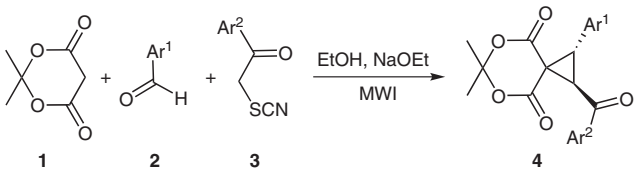
Key words: multicomponent reactions, cyclopropanes, stereoselectivity, microwave heating

The cyclopropane subunit plays an important role in organic chemistry because of its strained structure, interesting bonding characteristics, and value as an internal mechanistic probe.[1] It is also found as a basic structural unit that is widely present in a variety of naturally occurring compounds and rationally designed pharmaceutical agents with biological activity.[2] For these reasons, cyclopropanes have attracted much attention from organic chemists.[3,4]

The most important and useful methods for the preparation of cyclopropanes include Simmons–Smith cyclopropanation,[5] transition-metal-mediated carbene transfer from aliphatic diazo compounds to carbon–carbon double bonds,[6] the combination of ylides with electron-deficient olefins through Michael-initiated ring closure (MIRC),[7,8] and base-catalyzed cyclopropanation reactions between α-halogenated compounds and electron-deficient olefins.[9] Moreover, the observation that cyano-substituted alkenes can be converted into the corresponding cyclopropanes with high stereoselectivity has also attracted great attention.[8b,10] However, multicomponent reactions involving the stereoselective synthesis of cyclopropane-spirosubstituted Meldrum's acid have not been thoroughly explored. There are only a few reports on the preparation of spirosubstituted *cis*-1,2-cyclopropane, for example, the two-component reaction between arsonium salt and the benzylidene derivative of Meldrum's acid,[11a,b] or triphenylarsine-catalyzed reaction of bromides with the same benzylidene derivative.[11c] These reactions suffer from long reaction times, expensive and toxic catalysts, and narrow substrate scope. Therefore, the search continues for better derivatives of Meldrum's acid that can be used in a multicomponent strategy for the straightforward, economic, operationally simple, selective synthesis of spirosubstituted *trans*-cyclopropanes under mild, environmentally friendly conditions.

Over the past several years, our group has developed various multicomponent reactions (MCRs) that can provide easy access to useful functionalized multiple-ring structures of chemical and pharmaceutical interest.[12,13] For example, a new, four-component domino reaction was established as a way to provide easy access to the synthesis of multifunctionalized quinazoline derivatives.[12a] When aliphatic aldehydes were employed to replace their aromatic counterparts in the above reaction, the reaction was found to proceed along another pathway, leading to the formation of multi-functionalized tricyclo[6.2.2.0^{1,6}]dodecanes.[12b]

As a continuation of our research on the development of MCRs,[12,13] we would like to report another stereoselective three-component approach based on Meldrum's acid, that generates spirosubstituted *trans*-cyclopropane derivatives that are of chemical and biomedical importance. This reaction was achieved by reacting Meldrum's acid, aromatic aldehydes, and α-thiocyanate ketones in the presence of a catalytic amount of sodium ethoxide (NaOEt) under microwave irradiation, and avoided the use of ylides (Scheme 1).



1 2 3 4

Scheme 1

α-Thiocyanate ketones have attracted great attention as interesting intermediates due to their easy transformation into highly valuable molecules that can be applied to both organosulfur and heterocyclic chemistry.[14] Our strategy of synthesizing the highly multifunctionalized spirosubstituted *trans*-cyclopropane **4** through the reaction of Meldrum's acid with an aldehyde and α-thiocyanate ketones, was based on the fact that (1) Meldrum's acid (**1**) can be converted into the corresponding benzylidene derivative (**A**) through base-catalyzed reaction with aromatic aldehydes; (2) α-thiocyanate ketones **3**, which possess a strong nucleophilic center, favor reaction with the

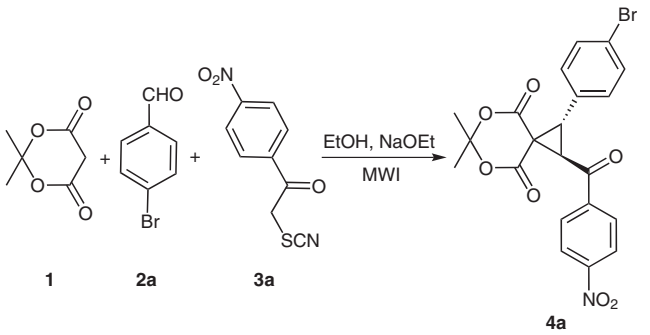
SYNTHESIS 2011, No. 15, pp 2459–2465
Advanced online publication: 08.07.2011
DOI: 10.1055/s-0030-1260096; Art ID: H34811SS

Meldrum's acid benzylidene derivative, providing the spirosubstituted *trans*-cyclopropanes because the thiocyanate acts as a good leaving group. This process avoids the use of arsenic reagent, thus minimizing environmental pollution.

Our initial experiments were focused on the one-pot, three-component reaction of Meldrum's acid (**1**), 1-(4-nitrophenyl)-2-thiocyanatoethanone (**3a**) and 4-bromobenzaldehyde (**2a**) using a range of inexpensive and readily available base catalysts under microwave irradiation (Table 1). It was found that when the reaction was carried out in ethanol using sodium ethoxide as a base catalyst, the desired product was obtained in a good yield (Table 1, entry 5). Other bases did not give such satisfactory results. The reaction was then performed in the presence of sodium ethoxide at a range of temperatures in a sealed vessel under microwave irradiation for 15 minutes. The yield of product **4a** was found to increase from 59 to 81% as the temperature was increased from 75 to 95 °C (Table 1, entry 6). However, a further increase in reaction temperature to 125 °C failed to improve the yield of product **4a**. As a result, the spirosubstituted *trans*-cyclopropanes can be synthesized in a one-pot, three-component reaction that avoids the need to separate intermediates and reduces the number of associated time-consuming and costly purification processes required.

After optimization of the conditions, to assess this approach, particularly in regard to library construction, the methodology was evaluated by using a range of α-thiocyanate ketones and aldehydes. As revealed in Table 2, commercially available aromatic aldehydes bearing chloro, fluoro, bromo or nitro groups were all found to be suitable for the reaction with Meldrum's acid (**1**) and α-thiocyanate ketones **3** to obtain electron-deficient *trans*-cyclopropanes in very good yields of 74–85% under microwave heating. We also utilized 1-(3-nitrophenyl)-2-thiocyanatoethanone instead of 1-(4-nitrophenyl)-2-thiocyanatoethanone for this reaction, and found that it can react with **1** and various aromatic aldehydes **2** to afford the corresponding spiro-cyclopropanes within 13–17 minutes in very good yields (76–87%). Unfortunately, both α-thiocyanate ketones with electron-donating groups and aldehydes with electron-donating groups failed to give the desired product **4**.

Table 1 Catalyst Optimization for the Synthesis of **4a**[a]



1 **2a** **3a** **4a**

Entry	Catalyst	Temp (°C)	Time (min)	Yield (%)[b]
1	none	75	15	trace
2	piperidine	75	15	14
3	K_2CO_3	75	15	20
4	Cs_2CO_3	75	15	29
5	NaOEt	75	15	59
6	NaOEt	95	15	81
7	NaOEt	125	15	78

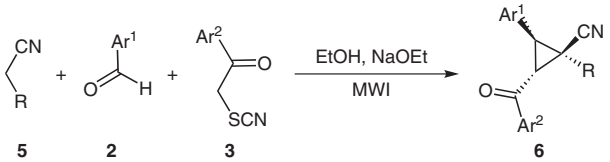
[a] Reactions performed in EtOH.
[b] Isolated yield.

Table 2 Synthesis of Compound **4** under Microwave Irradiation[a]

Entry	**4**	Ar^1	Ar^2	Time (min)	Yield (%)[b]
1	**4a**	4-BrC_6H_4	4-$O_2NC_6H_4$	15	81
2	**4b**	3,4-$Cl_2C_6H_4$	4-$O_2NC_6H_4$	17	85
3	**4c**	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	14	74
4	**4d**	3-FC_6H_4	4-$O_2NC_6H_4$	15	82
5	**4e**	4-FC_6H_4	3-$O_2NC_6H_4$	13	87
6	**4f**	3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	15	84
7	**4g**	4-$O_2NC_6H_4$	3-$O_2NC_6H_4$	16	85
8	**4h**	3-FC_6H_4	3-$O_2NC_6H_4$	15	81
9	**4i**	3-ClC_6H_4	3-$O_2NC_6H_4$	17	76
10	**4j**	3,4-$Cl_2C_6H_4$	3-$O_2NC_6H_4$	14	86

[a] Reaction conditions: NaOEt (0.3 equiv), 95 °C, EtOH, MW.
[b] Isolated yield.

In order to further expand the scope of the present method, Meldrum's acid was replaced by malononitrile or cyanoacetamide (Scheme 2). Although many methods have been reported for the synthesis of cyclopropanes,[8] all of the present methods are limited either by the inaccessibility of precursors, the requirement for multi-step processes, or by their operational complexity. Central to our approach was the development of a simple method, using readily available starting materials and simple experimental procedures, for the rapid synthesis of diverse cyclopropane derivatives.



5 **2** **3** **6**

Scheme 2

Seven aldehydes and four α-thiocyanate ketones were chosen to validate the approach through the construction

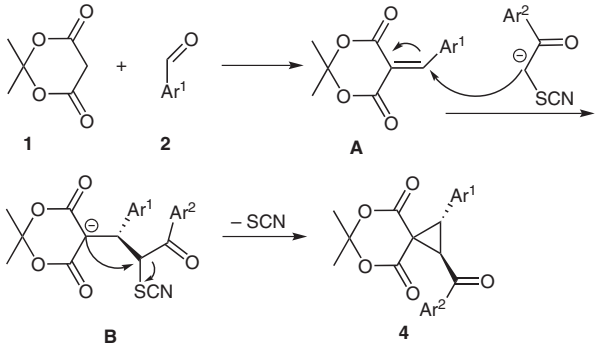
Table 3 Synthesis of Compounds **6** under Microwave Irradiation[a]

Entry	Product	Ar^1	Ar^2	R	Time (min)	Yield (%)[b]
1	**6a**	4-BrC_6H_4	Ph	CN	14	84
2	**6b**	4-ClC_6H_4	Ph	CN	14	82
3	**6c**	4-FC_6H_4	Ph	CN	13	81
4	**6d**	4-MeC_6H_4	Ph	CN	15	92
5	**6e**	4-$MeOC_6H_4$	Ph	CN	16	91
6	**6f**	4-HO-3-$O_2NC_6H_4$	Ph	CN	12	90
7	**6g**	4-BrC_6H_4	4-$MeOC_6H_4$	CN	13	88
8	**6h**	4-BrC_6H_4	4-ClC_6H_4	CN	15	86
9	**6i**	4-$O_2NC_6H_4$	Ph	$CONH_2$	18	89
10	**6j**	4-$O_2NC_6H_4$	3-ClC_6H_4	$CONH_2$	15	76

[a] Reaction conditions: K_2CO_3 (0.3 equiv), 95 °C, EtOH, MW.
[b] Isolated yield.

of a small library of cyclopropane derivatives. In all these cases, the reactions proceeded smoothly to give the corresponding cyclopropanes **6** in the presence of potassium carbonate in good yields; the results are summarized in Table 3.

The formation of **4** is expected to proceed through initial condensation of the aldehyde with Meldrum's acid to afford the arylidene derivative **A**, which further undergoes Michael addition in situ with α-thiocyanate ketones to yield intermediate **B**, which is then cyclized to afford the product **4** (Scheme 3).



Scheme 3

The structures of cyclopropanes **4** and **6** were confirmed by their IR, ^{1}H NMR, ^{13}C NMR and mass spectra. Furthermore, the attribution of relative stereochemistry was unequivocally determined by X-ray diffraction of a single crystal of **6a** (Figure 1).[15]

In summary, we have demonstrated a rapid and direct method for the one-pot, three-component synthesis of spiro-substituted *trans*-cyclopropanes as well as polysubstituted *trans*-cyclopropanes in good to excellent yields. The MCRs were conducted by reacting readily available and inexpensive starting materials under microwave irradiation. Particularly valuable features of this method include its operational simplicity, increased safety for small-scale, high-speed syntheses, and broader substrate scope.

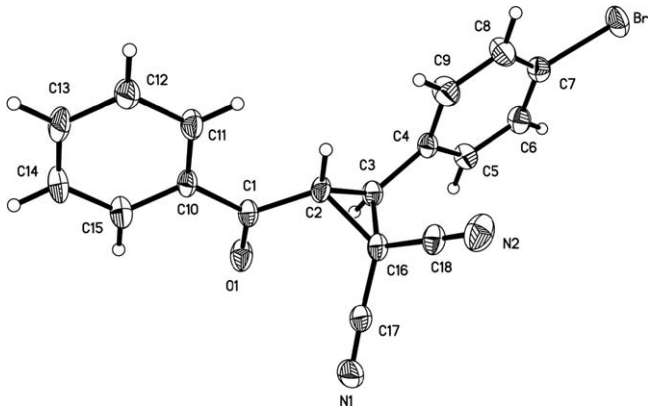


Figure 1 ORTEP diagram of **6a**

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded with an FTIR Tensor 27 spectrometer in KBr pellets and are reported in cm^{-1}. ^{1}H NMR spectra were measured with a Bruker DPX 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ (100 MHz, ^{13}C NMR) with chemical shifts (δ) given in ppm relative to TMS as internal standard. ESI-MS was determined with an LCQ Advantage HPLC/MS instrument (Thermo Finnigan). HRMS (ESI) were determined with a microTOF-QII HRMS/MS instrument (Bruker). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

Preparation of Electron-Deficient Cyclopropanes 4; General Procedure

In a 10-mL reaction vial, Meldrum's acid (**1**; 0.16 g, 1.1 mmol), aldehyde **2** (1 mmol), α-thiocyanate ketone **3** (1 mmol), NaOEt (0.02 g, 0.3 mmol) and EtOH (2.0 mL) were mixed and stirred at r.t.

The mixture was heated for 13–17 min at 95 °C under microwave irradiation. Upon completion (reaction monitored by TLC), the reaction mixture was cooled to r.t., the solid product was collected by Büchner filtration and washed with acetone to give the pure product **4**.

1-(4-Bromophenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4a)
Yield: 383 mg (81%); yellow solid; mp 237–239 °C.

IR (KBr): 3003, 1767, 1733, 1694, 1603, 1528, 1456, 1392, 1351, 1321, 1269, 1213, 1187, 1109, 1066, 1008, 997, 916, 854, 841, 819, 735 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, J = 8.4 Hz, 2 H, ArH), 8.15 (d, J = 8.8 Hz, 2 H, ArH), 7.63–7.58 (m, 4 H, ArH), 4.91 (d, J = 9.2 Hz, 1 H, CH), 4.24 (d, J = 9.2 Hz, 1 H, CH), 1.68 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.5, 164.3, 161.5, 150.1, 140.4, 132.1, 131.1, 130.0, 129.5, 124.1, 122.4, 112.7, 105.8, 42.8, 38.3, 27.6, 26.9.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{15}BrNO_7$: 471.9991; found: 472.0026.

1-(3,4-Dichlorophenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4b)
Yield: 394 mg (85%); yellow solid; mp 224–225 °C.

IR (KBr): 1766, 1731, 1694, 1604, 1556, 1528, 1481, 1449, 1393, 1379, 1340, 1314, 1279, 1225, 1110, 1066, 996, 921, 859, 842, 817, 744 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, J = 8.4 Hz, 2 H, ArH), 8.16 (d, J = 8.4 Hz, 2 H, ArH), 7.95 (s, 1 H, ArH), 7.71–7.67 (m, 2 H, ArH), 4.97 (d, J = 9.2 Hz, 1 H, CH), 4.29 (d, J = 9.6 Hz, 1 H, CH), 1.70 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 191.0, 178.8, 166.4, 163.4, 163.3, 150.6, 138.8, 131.9, 131.6, 129.5, 125.3, 125.2, 124.1, 105.9, 41.7, 38.5, 27.6, 26.9.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{14}Cl_2NO_7$: 462.0142; found: 462.0144.

6,6-Dimethyl-1-(4-nitrobenzoyl)-2-(4-nitrophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4c)
Yield: 326 mg (74%); yellow solid; mp 216–218 °C.

IR (KBr): 3116, 1767, 1732, 1694, 1604, 1526, 1454, 1390, 1349, 1321, 1271, 1212, 1110, 1067, 995, 917, 848, 792, 702 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.41 (d, J = 8.8 Hz, 2 H, ArH), 8.27 (d, J = 8.4 Hz, 2 H, ArH), 8.18 (d, J = 8.8 Hz, 2 H, ArH), 7.94 (d, J = 8.8 Hz, 2 H, ArH), 5.02 (d, J = 9.6 Hz, 1 H, CH), 4.42 (d, J = 9.2 Hz, 1 H, CH), 1.70 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.2, 164.1, 161.5, 150.2, 147.6, 140.3, 138.4, 131.4, 129.6, 124.1, 123.1, 106.0, 41.7, 38.7, 27.7, 26.9.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{15}N_2O_9$: 439.0772; found: 439.0740.

1-(3-Fluorophenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4d)
Yield: 339 mg (82%); yellow solid; mp 210–212 °C.

IR (KBr): 1767, 1733, 1693, 1625, 1528, 1490, 1456, 1396, 1385, 1323, 1285, 1202, 1065, 998, 920, 842, 782, 760, 716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 1 H, ArH), 8.48 (d, J = 8.4 Hz, 1 H, ArH), 8.28 (d, J = 7.6 Hz, 1 H, ArH), 7.74 (t, J = 8.0 Hz, 1 H, ArH), 7.43–7.35 (m, 3 H, ArH), 7.34–7.30 (m, 1 H, ArH), 4.40 (d, J = 9.6 Hz, 1 H, CH), 4.05 (d, J = 9.2 Hz, 1 H, CH), 1.77 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.4, 164.3, 161.8 ($^1J_{C–F}$ = 241.7 Hz), 161.4, 150.2, 140.4, 133.4 ($^3J_{C–F}$ = 8.4 Hz), 130.1 ($^3J_{C–F}$ = 8.5 Hz), 129.5, 126.4 ($^4J_{C–F}$ = 2.4 Hz), 124.1, 116.7 ($^2J_{C–F}$ = 22.9 Hz), 115.7 ($^2J_{C–F}$ = 21.0 Hz), 105.8, 42.7, 38.3, 27.5, 26.9.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{15}FNO_7$: 412.0827; found: 412.0826.

1-(4-Fluorophenyl)-6,6-dimethyl-2-(3-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4e)
Yield: 359 mg (87%); yellow solid; mp 164–166 °C.

IR (KBr): 3042, 1771, 1739, 1694, 1615, 1534, 1518, 1475, 1455, 1394, 1353, 1310, 1267, 1227, 1207, 1176, 1094, 1057, 1025, 999, 920, 837, 782, 730, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.64 (s, 1 H, ArH), 8.51 (d, J = 8.0 Hz, 1 H, ArH), 8.39–8.33 (m, 1 H, ArH), 7.90 (t, J = 8.0 Hz, 1 H, ArH), 7.71 (dd, J = 5.5, 8.4 Hz, 2 H, ArH), 7.25 (t, J = 8.8 Hz, 2 H, ArH), 4.96 (d, J = 9.2 Hz, 1 H, CH), 4.27 (d, J = 9.6 Hz, 1 H, CH), 1.68 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.9, 164.3, 162.3 ($^1J_{C–F}$ = 244.4 Hz), 161.5, 148.0, 137.1, 134.2, 132.2 ($^3J_{C–F}$ = 8.4 Hz), 130.8, 127.8, 126.8 ($^4J_{C–F}$ = 2.7 Hz), 122.4, 115.7 ($^2J_{C–F}$ = 21.5 Hz), 105.7, 42.9, 38.1, 27.5, 26.9.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{15}FNO_7$: 412.0827; found: 412.0828.

6,6-Dimethyl-1-(3-nitrobenzoyl)-2-(3-nitrophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4f)
Yield: 370 mg (84%); yellow solid; mp 230–231 °C.

IR (KBr): 3086, 3005, 1760, 1736, 1696, 1615, 1536, 1489, 1437, 1397, 1352, 1319, 1264, 1227, 1200, 1094, 1063, 1000, 918, 841, 709 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.68–8.67 (m, 1 H, ArH), 8.58 (s, 1 H, ArH), 8.52 (dd, J = 1.6, 8.0 Hz, 1 H, ArH), 8.38 (d, J = 8.0 Hz, 1 H, ArH), 8.25 (dd, J = 8.0, 1.6 Hz, 1 H, ArH), 8.16 (d, J = 7.6 Hz, 1 H, ArH), 7.90 (t, J = 8.0 Hz, 1 H, ArH), 7.73 (t, J = 8.0 Hz, 1 H, ArH), 5.13 (d, J = 9.6 Hz, 1 H, CH), 4.47 (d, J = 9.6 Hz, 1 H, CH), 1.71 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.7, 164.0, 161.7, 148.0, 147.7, 137.0, 136.8, 134.3, 133.2, 130.8, 129.7, 127.8, 124.6, 123.6, 122.6, 112.7, 105.9, 41.6, 38.4, 27.7, 27.0.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{15}N_2O_9$: 439.0772; found: 439.0737.

6,6-Dimethyl-1-(3-nitrobenzoyl)-2-(4-nitrophenyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4g)
Yield: 374 mg (85%); yellow solid; mp 221–223 °C.

IR (KBr): 3089, 1774, 1743, 1698, 1614, 1535, 1520, 1449, 1396, 1346, 1304, 1264, 1221, 1207, 1177, 1088, 1054, 1022, 995, 922, 849, 707 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.67–8.65 (m, 1 H, ArH), 8.54–8.51 (m, 1 H, ArH), 8.39–8.36 (m, 1 H, ArH), 8.27 (d, J = 8.8 Hz, 2 H, ArH), 7.95 (d, J = 8.8 Hz, 2 H, ArH), 7.90 (t, J = 8.0 Hz, 1 H, ArH), 5.07 (d, J = 9.6 Hz, 1 H, CH), 4.44 (d, J = 9.6 Hz, 1 H, CH), 1.70 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.6, 164.0, 161.6, 148.0, 147.6, 138.4, 136.9, 134.3, 131.4, 130.9, 127.9, 123.1, 122.6, 119.6, 105.9, 41.6, 38.4, 27.7, 27.0.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{21}H_{15}N_2O_9$: 439.0772; found: 439.0800.

1-(3-Fluorophenyl)-6,6-dimethyl-2-(3-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4h)
Yield: 335 mg (81%); yellow solid; mp 232–233 °C.

IR (KBr): 3084, 1759, 1737, 1697, 1615, 1592, 1537, 1477, 1445, 1397, 1385, 1353, 1314, 1284, 1234, 1215, 1152, 1089, 1064, 1023, 1000, 912, 899, 865, 808, 790 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1 H, ArH), 8.49 (dd, *J* = 0.8, 8.0 Hz, 1 H, ArH), 8.27 (d, *J* = 7.6 Hz, 1 H, ArH), 7.74 (t, *J* = 8.0 Hz, 1 H, ArH), 7.51 (m, 2 H, ArH), 7.28 (s, 2 H, ArH), 4.36 (d, *J* = 9.6 Hz, 1 H, CH), 4.02 (d, *J* = 9.2 Hz, 1 H, CH), 1.78 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.9, 164.3, 161.8 ($^1J_{C-F}$ = 241.4 Hz), 161.5, 148.0, 137.0, 134.3, 133.4 ($^3J_{C-F}$ = 8.3 Hz), 130.8, 130.1 ($^3J_{C-F}$ = 8.5 Hz), 127.9, 126.4 ($^4J_{C-F}$ = 2.3 Hz), 122.5, 116.7 ($^2J_{C-F}$ = 22.8 Hz), 115.7 ($^2J_{C-F}$ = 20.4 Hz), 105.8, 42.5, 37.9, 27.5, 26.9.

HRMS (ESI): *m*/*z* [M – H]$^+$ calcd for $C_{21}H_{15}FNO_7$: 412.0827; found: 412.0800.

1-(3-Chlorophenyl)-6,6-dimethyl-2-(3-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4i)
Yield: 326 mg (76%); yellow solid; mp 222–223 °C.

IR (KBr): 3087, 1761, 1739, 1694, 1628, 1535, 1444, 1397, 1352, 1315, 1282, 1263, 1223, 1201, 1092, 1061, 1021, 1000, 922, 877, 839, 792, 734, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1 H, ArH), 8.48 (m, 1 H, ArH), 8.29 (d, *J* = 7.6 Hz, 1 H, ArH), 7.74 (t, *J* = 7.6 Hz, 1 H, ArH), 7.40 (dd, *J* = 7.4, 13.7 Hz, 1 H, ArH), 7.22 (d, *J* = 8.0 Hz, 1 H, ArH), 7.14–7.09 (m, 2 H, ArH), 4.40 (d, *J* = 9.6 Hz, 1 H, CH), 4.06 (d, *J* = 9.2 Hz, 1 H, CH), 1.77 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.8, 164.2, 161.5, 148.0, 137.0, 134.2, 133.2, 132.9, 130.8, 129.9, 129.6, 129.0, 127.8, 122.5, 112.7, 105.8, 42.3, 38.0, 27.6, 27.0.

HRMS (ESI): *m*/*z* [M – H]$^+$ calcd for $C_{21}H_{15}ClNO_7$: 428.0521; found: 428.0511.

1-(3,4-Dichlorophenyl)-6,6-dimethyl-2-(3-nitrobenzoyl)-5,7-dioxaspiro[2.5]octane-4,8-dione (4j)
Yield: 398 mg (86%); yellow solid; mp 229–230 °C.

IR (KBr): 3081, 1760, 1738, 1697, 1615, 1580, 1539, 1478, 1450, 1395, 1351, 1311, 1280, 1225, 1202, 1136, 1088, 1063, 1035, 998, 923, 910, 872, 806 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 1 H, ArH), 8.51–8.49 (m, 1 H, ArH), 8.32–8.28 (m, 2 H, ArH), 7.76 (t, *J* = 8.0 Hz, 2 H, ArH), 7.64 (t, *J* = 7.6 Hz, 1 H, ArH), 4.45 (d, *J* = 9.2 Hz, 1 H, CH), 4.19 (d, *J* = 9.2 Hz, 1 H, CH), 1.79 (s, 3 H, CH_3), 1.75 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.7, 164.1, 161.6, 148.0, 136.9, 134.3, 131.9, 131.8, 131.6, 130.9, 130.8, 130.5, 130.3, 127.9, 122.5, 105.8, 41.5, 38.1, 27.6, 27.0.

HRMS (ESI): *m*/*z* [M – H]$^+$ calcd for $C_{21}H_{14}Cl_2NO_7$: 462.0142; found: 462.0143.

Preparation of Cyclopropanes 6; General Procedure
In a 10-mL Emrys reaction vial, the malononitrile or cyanoacetamide **5** (1.5 mmol), aldehyde **2** (1 mmol), α-thiocyanate ketone **3** (1 mmol), K_2CO_3 (0.04 g, 0.3 mmol) and EtOH (2.0 mL) were mixed and stirred at r.t. The mixture was heated for 12–18 min at 95 °C under microwave irradiation. Upon completion (reaction monitored by TLC), the reaction mixture was cooled to r.t. and the solid product was collected by Büchner filtration and subsequently washed with acetone to give the pure product **6**.

2-Benzoyl-3-(4-bromophenyl)cyclopropane-1,1-dicarbonitrile (6a)[8c]
Yield: 294 mg (84%); yellow solid; mp 156–158 °C (Lit.[8c] 169–170 °C).

2-Benzoyl-3-(4-chlorophenyl)cyclopropane-1,1-dicarbonitrile (6b)[8d]
Yield: 251 mg (82%); yellow solid; mp 165–168 °C (Lit.[8d] 175–176 °C).

2-Benzoyl-3-(4-fluorophenyl)cyclopropane-1,1-dicarbonitrile (6c)[8e]
Yield: 235 mg (81%); yellow solid; mp 151–152 °C (Lit.[8e] 156 °C).

2-Benzoyl-3-*p*-tolylcyclopropane-1,1-dicarbonitrile (6d)[8c]
Yield: 263 mg (92%); yellow solid; mp 156–157 °C (Lit.[8c] 161–162 °C).

2-Benzoyl-3-(4-methoxyphenyl)cyclopropane-1,1-dicarbonitrile (6e)
Yield: 275 mg (91%); yellow solid; mp 154–156 °C.

IR (KBr): 3039, 2246, 1679, 1613, 1598, 1581, 1519, 1493, 1468, 1450, 1408, 1344, 1297, 1254, 1228, 1183, 1029, 1000, 835, 821, 741, 683, 653, 631 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.27–8.25 (m, 2 H, ArH), 7.79 (t, *J* = 7.6 Hz, 1 H, ArH), 7.68–7.61 (m, 4 H, ArH), 7.01 (d, *J* = 8.8 Hz, 2 H, ArH), 5.00 (d, *J* = 8.4 Hz, 1 H, CH), 4.03 (d, *J* = 8.4 Hz, 1 H, CH), 3.80 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.4, 159.9, 135.3, 134.7, 130.4, 129.0, 122.2, 114.0, 113.0, 112.9, 55.2, 38.4, 34.8, 15.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{14}N_2NaO_2$: 325.0948; found: 325.0939.

2-Benzoyl-3-(4-hydroxy-3-nitrophenyl)cyclopropane-1,1-dicarbonitrile (6f)
Yield: 300 mg (90%); yellow solid; mp 212–214 °C.

IR (KBr): 3095, 2248, 1676, 1630, 1594, 1542, 1494, 1447, 1414, 1345, 1325, 1258, 1230, 1177, 1080, 980, 845, 753, 706, 687 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.35 (s, 1 H, OH), 8.30–8.27 (m, 3 H, ArH), 7.88 (dd, *J* = 2.0, 8.8 Hz, 1 H, ArH), 7.81–7.77 (m, 1 H, ArH), 7.66 (t, *J* = 8.0 Hz, 2 H, ArH), 7.19 (d, *J* = 8.8 Hz, 1 H, ArH), 5.11 (d, *J* = 8.0 Hz, 1 H, CH), 4.12 (d, *J* = 8.0 Hz, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.0, 152.2, 13.7, 135.7, 135.3, 134.7, 129.1, 129.0, 125.9, 121.7, 119.1, 112.8, 112.6, 37.1, 34.7, 15.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{12}N_3O_4$: 334.0823; found: 334.0833.

2-(4-Bromophenyl)-3-(4-methoxybenzoyl)cyclopropane-1,1-dicarbonitrile (6g)
Yield: 334 mg (88%); yellow solid; mp 153–154 °C.

IR (KBr): 3034, 2251, 1659, 1604, 1573, 1512, 1494, 1428, 1391, 1341, 1260, 1173, 1113, 1074, 1012, 957, 850, 791, 743, 626 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.27 (d, *J* = 8.8 Hz, 2 H, ArH), 7.67 (s, 4 H, ArH), 7.17 (d, *J* = 8.8 Hz, 2 H, ArH), 5.03 (d, *J* = 8.4 Hz, 1 H, CH), 4.07 (d, *J* = 8.0 Hz, 1 H, CH), 3.91 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.6, 164.0, 160.3, 132.7, 132.1, 131.0, 130.4, 128.3, 127.1, 114.2, 114.0, 113.0, 82.3, 55.7, 41.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}BrN_2O_2$: 381.0234; found: 381.0248.

2-(4-Bromophenyl)-3-(4-chlorobenzoyl)cyclopropane-1,1-dicarbonitrile (6h)
Yield: 330 mg (86%); yellow solid; mp 144–146 °C.

IR (KBr): 3073, 2258, 1667, 1592, 1490, 1425, 1403, 1331, 1299, 1250, 1179, 1092, 1068, 1009, 968, 882, 845, 821, 781, 713 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.30 (d, *J* = 8.4 Hz, 2 H, ArH), 7.73 (d, *J* = 8.4 Hz, 2 H, ArH), 7.67 (s, 4 H, ArH), 5.07 (d, *J* = 8.4 Hz, 1 H, CH), 4.09 (d, *J* = 8.4 Hz, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.3, 139.7, 134.1, 131.5, 131.3, 131.0, 130.1, 129.1, 122.6, 112.7, 112.6, 37.9, 34.4, 15.5.

HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{18}H_9BrClN_2O$: 382.9581; found: 382.9575.

2-Benzoyl-1-cyano-3-(4-nitrophenyl)cyclopropanecarboxamide (6i)
Yield: 298 mg (89%); yellow solid; mp 213–214 °C.

IR (KBr): 3439, 3398, 3308, 3200, 2185, 1687, 1646, 1622, 1578, 1507, 1448, 1348, 1306, 1246, 1186, 1107, 1040, 978, 894, 849, 785 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.4 Hz, 2 H, ArH), 7.84 (d, *J* = 7.6 Hz, 2 H, ArH), 7.65–7.57 (m, 3 H, ArH), 7.49 (t, *J* = 7.6 Hz, 2 H, ArH), 5.21 (d, *J* = 4.4 Hz, 1 H, CH), 4.97 (d, *J* = 4.8 Hz, 1 H, CH), 4.84 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.5, 161.8, 149.5, 146.9, 134.3, 133.6, 128.9, 128.8, 128.7, 123.8, 117.9, 70.0, 55.2, 50.2.

HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{18}H_{12}N_3O_4$: 334.0822; found: 334.0821.

2-(3-Chlorobenzoyl)-1-cyano-3-(4-nitrophenyl)cyclopropanecarboxamide (6j)
Yield: 280 mg (76%); yellow solid; mp 236–238 °C.

IR (KBr): 3413, 3327, 3222, 2186, 1692, 1636, 1568, 1512, 1409, 1347, 1221, 1109, 1014, 981, 889, 805, 745, 689 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.28 (d, *J* = 8.8 Hz, 2 H, ArH), 8.02 (s, 1 H, ArH), 7.93 (d, *J* = 7.6 Hz, 1 H, ArH), 7.74–7.68 (m, 3 H, ArH), 7.56 (t, *J* = 8.0 Hz, 1 H, ArH), 7.33 (s, 2 H, NH_2), 5.36 (d, *J* = 2.0 Hz, 1 H, CH), 4.88 (d, *J* = 1.8 Hz, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 191.8, 161.6, 149.4, 146.9, 136.4, 133.8, 133.3, 130.8, 128.9, 128.3, 127.3, 123.8, 117.9, 70.0, 55.3, 50.1.

HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{18}H_{11}ClN_3O_4$: 368.0432; found: 368.0411.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

We are grateful for financial support from the National Science Foundation of China (21072163 and 21002083), PAPD of Jiangsu Higher Education Institutions, Sci. Foundation in Interdisciplinary Major Res. Project of XZNU (No. 09XKXK01), and Graduate Foundation of XZNU (No. 2010YLB031).

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