Diphenylammonium Triflate: A Novel and Efficient Catalyst for Synthesis of Spiro-Heterocyclic Compounds

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Abstract: A general and practical one-pot synthesis of spiro-heterocyclic compounds using diphenylammonium triflate (DPAT, 5 mol%) as a novel and efficient catalyst is described. The pseudo four-components Biginelli-like reaction of 5,5-dimethyl-1,3-cyclohexanedione, thiourea and aldehydes catalyzed by DPAT in refluxing ethanol produced the corresponding spiro-heterocyclic compounds with moderate to good yields. A possible mechanism is proposed.

Keywords: Biginelli-type reaction, spiro-heterocyclic compounds, catalyst, diphenylammonium triflate.

INTRODUCTION

The classical Biginelli [1] three-component condensation reaction is typically the acid-catalyzed [2] cyclocondensation of an aldehyde, a urea or thiourea and a β-dicarbonyl compound, result in 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), which are efficient calcium channel modulators [3], mitotic kinesine inhibitors [4], antibacterial and antiviral agents [4,5]. In recent years, Biginelli reaction has been widely used for generating large collections of molecules in combinatorial synthesis [6]. In addition, the novel pseudo four-component Biginelli-type scaffold synthesis, the use of the cyclic β-dicarbonyl compounds instead of open-chain dicarbonyl compounds has attracted a synthetic interest for the formation of spiro-heterocyclic structure catalyzed by HCl [7], $NaHSO_4$ [8], $H_3PW_{12}O_{40}$ [9] and TMSCl [10]. However it suffers from harsh reaction conditions, unsatisfactory yields and unsuitable environment calls. Moreover, these catalysts are limited to cyclic-diketones and none of the reports are extended to the use of open-chain dicarbonyl compounds in classic Biginelli reaction conditions.

In continuation of our interest in applications of Biginelli reaction and the metal triflates [11], which were widely used in organic synthesis, we wish to report a novel and efficient catalyst diphenylammonium triflate (DPAT) for prompting the Biginelli-type reaction of aldehydes, thiourea and 5,5-dimethyl-1,3-cyclohexanedione under mild conditions. The reaction proceeded smoothly to give the spiro-heterocyclic compound **1** in moderate to good yield. The catalyst DPAT [12] had low toxicity, high stability, easy preparation by a simple acid-base reaction of diphenylamine and trifluoromethanesulfonic acid in toluene at ice bath.

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RESULT AND DISCUSSION

Firstly, we tried to find the optimal catalyst for the formation of spiro-heterocycles **1**. The model reaction of 5,5-dimethyl-1,3-cyclohexanedione **3**, thiourea **4** and benzaldehyde **5a** (Scheme **1**) was performed in the presence of Lewis catalysts in refluxing EtOH. The results were summarized in Table **1**. According to Table **1**, title product **1a** was not obtained with $NaHSO_4$ or no catalyst in the reaction (Table **1**, entries 1, 2), which gave the DHPM **2a** in good yield. Moreover, the reaction was insufficient to afford the target product **1a** catalyzed by CF_3CO_2H, L-proline and $Sr(OTf)_2$ (Table **1**, entries 3-5). The optimal catalyst was DPAT, which gave the highest yield of target product **1a** in 62 % yield (Table **1**, entry 6). Excitedly, only 5 mol% of DPAT was sufficient for the reaction (Table **1**, entry 7).

In order to confirm the optimum reaction conditions for the model reaction catalyzed by DPAT, various factors including molar ratio, solvent and reaction temperature were investigated. The results were listed in Table **2**.

Initially, the experiments were performed in various solvents in the presence of DPAT and the results were showed in Table **2**. It was found that the reaction is affected remarkably by solvents. We got low yield of **1a** in MeCN, toluene, DMF or $CHCl_3$ (Table **2**, entries 1-4) and the best solvent was EtOH (Table **2**, entry 5). Moreover, increasing the reaction temperature was a benefit to improving the yield of the product (Table **2**, entries 5-7). In addition, the reaction was influenced greatly by the molar ratio of reagents. The results indicated that the amount of benzaldehyde **5a** was a key factor to afford the target product **1a** compared with traditional Biginelli reactions. Excessive benzaldehyde **5a** was necessary to afford the title product **1a** (Table **2**, entries 5, 8) and the best molar ratio of substrates (**3** : **4** : **5a**) was 1 : 1 : 5. Lower ratio of reagents (**3** : **4** : **5a** = 1 : 1 : 1.5 or 3) could not produce the desired product **1a**; in contrast, the classical Biginelli product **2a** was obtained in excellent yield (Table **2**, entries 9, 10).

As the results indicated in Table **1** and Table **2**, the optimal conditions for the reaction were in the presence of 5

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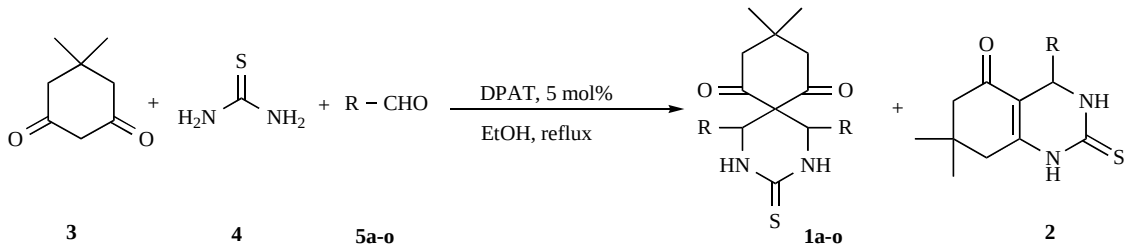


3 **4** **5a-o** **1a-o** **2**

Scheme 1.

Table 1. The Reaction of 5,5-Dimethyl-1,3-cyclohexanedione 3, Thiourea 4 and Benzaldehyde 5a in Presence of Various Acidic Catalysts[a]

Entry	Catalyst	Catalyst Amount (mol %)	Product 1a (Yield, %)[b]	Product 2a (Yield, %)[b]
1	$NaHSO_4$	20	--	87
2	None	--	--	72
3	CF_3CO_2H	20	47	35
4	L-Proline	20	53	28
5	$Sr(OTf)_2$	20	35	46
6	DPAT	20	62	29
7	DPAT	5	62	25
8	DPAT	1	54	28

[a]Reactions conditions: 5,5-dimethyl-1,3-cyclohexanedione **3** (1.0 mmol), thiourea **4** (1.0 mmol), benzaldehyde **5a** (5.0 mmol) in refluxing EtOH.[b]Isolated yield.

Table 2. The Influence of the Reaction Conditions on the Product Yield for the Model Reaction Catalyzed by DPAT[a]

Entry	Solvent	Molar Ratio[b]	Temp. (^oC)	Yield of 1a (%)[c]	Yield of 2a (%)[c]
1	MeCN	1 : 1 : 5	reflux	40	43
2	Toluene	1 : 1 : 5	80	25	67
3	DMF	1 : 1 : 5	80	36	35
4	$CHCl_3$	1 : 1 : 5	reflux	10	76
5	EtOH	1 : 1 : 5	reflux	62	25
6	EtOH	1 : 1 : 5	r. t.	16	56
7	EtOH	1 : 1 : 5	50	25	72
8	EtOH	1 : 1 : 4	reflux	42	47
9	EtOH	1 : 1 : 3	reflux	--	89
10	EtOH	1 : 1 : 1.5	reflux	--	92

[a]All the reactions was catalyzed by 5 mol% DPAT and were sonicated firstly for dissolving. [b]The molar ratio was **3** : **4** : **5a**. [c]Isolated yield.

mol% DPAT in refluxing EtOH with the 1:1:5 of reagents (**3** : **4** : **5a**).

With the optimal condition in hand, various aldehydes were examined in this reaction (Scheme **1**). The results were summarized in Table **3**. All reactions went smoothly under mild reaction conditions to produce **1** in moderate to good yield.

From Table **3**, the reaction proceeded very efficiently with *meta*-substituted benzaldehydes and disubstituted benzaldehydes (Table **3**, entries 3-8) carrying either electron-donating or electron-withdrawing group in good yield (75%-80%), except *meta*-substituted benzaldehyde with hydroxy group (Table **3**, entry 2), which gave moderate yield (60%) of **1b** and a small amount of **2b**. However, benzaldehyde and 4-methylbenzaldehyde exhibited the different chemical behaviors to this reaction (Table **3**, entries 1, 9), which afforded a moderate yield of **1** and a little amount of **2**. Moreover, *para*-substituted benzaldehydes carrying F, Cl and OMe (Table **3**, entries 10-12) got the classical Biginelli products **2** as the major products and the target product **1** was obtained in low yield (35%-40%). There was no desired product **1m** afforded with *ortho*-substituted benzaldehyde due to the steric hindrance (Table **3**, entry 13). Based on the above results, we attempted to extend the methodology to heterocyclo aldehydes and aliphatic aldehydes.

Unfortunately, trace amount of target product **1n** was obtained with thiophene (Table **3**, entry 14) and no product was detected with aliphatic aldehyde (Table **3**, entry 15).

From the above results and literatures [7, 13], a possible explanation for the formation of spiro-heterocyclic compounds **1** is shown in Scheme **2**. Firstly, aldehyde and thiourea would easily form the intermediate acyl imine **6**, followed by a Michael-type addition reacting with a β-diketo enolate **9** to give the open chain ureide **7**. Subsequently, two trends for intermediate **7** are presented in Scheme **2**. Path A was cyclization to afford classical Biginelli product **2**. Path B involved condensation of aldehyde to form intermediate **8** and ultimately cyclize to the spiro-heterocyclic compound **1**.

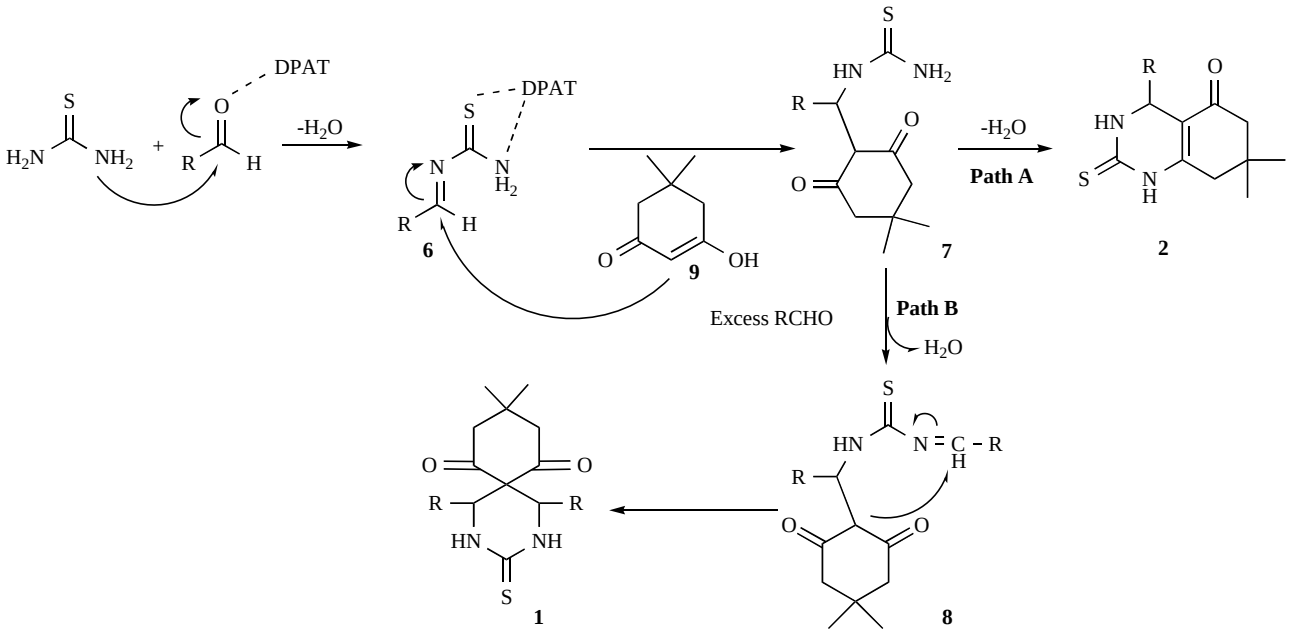
CONCLUSION

In summary, we have developed an efficient one-pot synthesis of spiro-fused heterobicyclic compouds (**1**) by using a novel catalyst DPAT. Contrary to classic Biginelli reaction, this methodology showed that the ratio of substrates was the main reaction factor in these reactions.

Table 3. Synthesis of Spiro-Heterocyclic Compounds 1[a]

Entry	R	Time (h)	Product (1)	Yield (%)[b]
1	5a: C_6H_5	6	1a	62[c]
2	5b: 3-HOC_6H_4	5	1b	60[c]
3	5c: 3-FC_6H_4	4	1c	77
4	5d: 3-ClC_6H_4	4	1d	79
5	5e: 3-$MeOC_6H_4$	4	1e	80
6	5f: 3-$NO_2C_6H_4$	6	1f	76
7	5g: 3,4-$(CH_3)_2C_6H_3$	5	1g	75
8	5h: 3-MeO-4-HOC_6H_3	5	1h	76
9	5i: 4-MeC_6H_4	6	1i	65[c]
10	5j: 4-$MeOC_6H_4$	7	1j	35[c]
11	5k: 4-FC_6H_4	8	1k	40[c]
12	5l: 4-ClC_6H_4	8	1l	43[c]
13	5m: 2-ClC_6H_4	7	1m	--[c]
14	5n: Thiophene	7	1n	trace[c]
15	5o: t-Bu	10	1o	--[d]

[a]Reactions conditions: 5,5-dimethyl-1,3-cyclohexanedione **3** (1.0 mmol), thiourea **4** (1.0 mmol), aldehyde **5** (5.0 mmol) and DPAT (0.05 mmol, 5 mol%), in refluxing EtOH. [b]Isolated yield. [c]Besides the product **1**, there was another product **2** obtained in these reactions. [d]No product obtained.



Scheme 2.

Moreover, the method offered in this paper had merits of the present process including good yields, environment friendly procedure and easy isolation. Therefore, it offers an important method for ammonium triflate involving Biginelli-like reaction and further studies are in progress.

EXPERIMENTAL

General

Analytical grade solvents and commercially available reagents were used without further purification. Melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Aviatar-370 instrument, spectrometer using samples as neat liquids or as KBr plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian (400 MHz) instrument using TMS as an internal standard. ^{19}F NMR spectra were measured at Varian (376 MHz) and Anance III (470.6 MHz) and chemical shifts were given relative to CF_3COOH. Mass spectra were measured with Agilent 6210 TOF LC/MS.

General Procedure for the Preparation of 1a-l

5,5-Dimethyl-1,3-cyclohexanedione **3** (1 mmol), thiourea **4** (1 mmol), aldehyde **5** (5 mmol) and DPAT (0.05 mmol) were added in EtOH (1.5 mL). The reaction mixture was sonicated at room temperature for dissolving and subsequently heated at reflux. Solid precipitated was formed after the completion of the reaction. The mixture was poured into 20 g crushed ice. Crude product was recrystallized from EtOH to give pure product **1**.

1,5-Diphenyl-3-thioxo-9,9-dimethyl-2,4-diazaspir-spiro [5,5]undecane-7,11-dione (1a)

White solid. Yield: 62%, mp: 230.0-230.5 °C. IR (KBr) ν_{max}: 3360, 3164, 1682, 1558, 1490, 1400, 1196, 763, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.34 (m, 6 H), 7.2-7.21 (m, 4 H), 6.75 (s, 2 H), 5.17 (s, 2 H), 1.80 (s, 2 H), 1.79 (s, 2 H), 0.10 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.1, 204.8, 177.5, 134.8, 129.9, 129.3, 128.5, 63.5, 55.9, 54.4, 29.0, 28.4. HRMS (ESI-TOF) calcd. for $C_{23}H_{24}N_2NaO_2S$ ([M + Na]$^+$): 415.1456; Found: 415.1449.

1,5-Bis(3-fluorophenyl)-3-thioxo-9,9-dimethyl-2,4-diaza-spir-spiro[5,5]undecane-7,11-dione (1c)

White solid. Yield 77%, mp: 207.8-208.4 °C. IR (KBr) ν_{max}: 3419, 3166, 1695, 1616, 1553, 1504, 1401, 1188, 797 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.81 (s, 2 H), 7.41 (q, J = 7.6, 14.8 Hz, 2 H), 7.20 (t, J = 8.0 Hz, 2 H), 6.91 (d, J = 7.6 Hz, 2 H), 6.86 (d, J = 10.0 Hz, 2 H), 5.15 (s, 2 H), 1.76 (s, 2 H), 1.73 (s, 2 H), 0.08 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 208.4, 204.9, 177.0, 162.9, 160.5, 137.8, 137.7, 130.6, 130.5, 125.1, 116.1, 115.9, 115.7, 115.5, 64.4, 61.8, 55.5, 53.6, 28.6, 27.7. HRMS (ESI-TOF) calcd. for $C_{23}H_{23}F_2N_2O_2S$ ([M + H]$^+$): 429.1448; Found: 429.1439.

1,5-Bis(4-chlorophenyl)-3-thioxo-9,9-dimethyl-2,4-diaza-spir-spiro[5,5]undecane-7,11-dione (1l)

White solid. Yield 43%, mp: 195.0-195.5 °C. IR (KBr) ν_{max}: 3418, 3143, 1687, 1560, 1490, 1401, 1199, 1091, 825 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74 (s, 2 H), 7.44 (d, J = 8.0 Hz, 4 H), 7.09 (d, J = 8.4 Hz, 4 H), 5.12 (s, 2 H), 1.75 (s, 2 H), 1.70 (s, 2 H), 0.09 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 208.5, 204.8, 177.0, 134.1, 133.5, 130.6, 128.4, 64.5, 61.7, 55.5, 53.7, 28.6, 27.8. HRMS (ESI-TOF) calcd. for $C_{23}H_{23}Cl_2N_2O_2S$ ([M + H]$^+$): 461.0857; Found: 461.0851.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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