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An Efficient Intramolecular Stetter Reaction in Room Temperature Ionic Liquids Promoted By Microwave Irradiation

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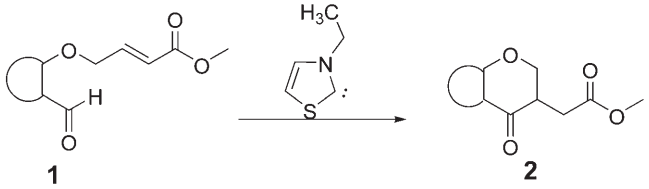
Abstract: This communication describes the first report of a microwave-assisted intramolecular Stetter reaction using imidazolium-type room temperature ionic liquids (RTILs) as solvents, with thiazolium salts and Et_3N as catalysts. The features such as good to excellent yields, shorter reaction time (5–20 min), and recyclable and reusable ionic liquid and catalyst make this method an environmentally benign and highly efficient procedure for the preparation of chromanone derivatives.

Keywords: chroman-4-ones; ionic liquids; microwave heating; Stetter reaction

The Stetter reaction, the addition of an activated aldehyde to an acceptor bearing an activated double bond (Scheme 1), is a very simple and useful method for the synthesis of 1,4-bifunctional compounds, which are key intermediates in organic synthesis.[1,2] The Stetter reaction is traditionally performed in protic solvents like alcohol or in aprotic ones such as DMF, dioxane, and acetonitrile. Solvent-free conditions have also been used for the Stetter reaction. Since the first report by Stetter in 1973,[1b] this reaction has been widely used to synthesize cyclopentenones[3] and heterocycles,[4] and extended recently to electrophilic olefins anchored either on a solid support[2b,c] or onto "task-specific ionic liquids".[5] In addition, asymmetric Stetter reactions have also been reported with enantioselectivities up to 95% in some cases.[6] More recently, room temperature ionic liquids (RTILs) have been used for the Stetter reaction, which gave higher yields (50–78%) than those obtained in classical organic solvents,[7] however, it is impossible to recycle the catalyst, and the reaction always take a long time (over 22 h) to fully consume the substrates.



Scheme 1.

Microwave irradiation has been proven to be a powerful technique for promoting a variety of chemical reactions.[8] The main benefits of performing reactions under microwave irradiation conditions are significant rate-enhancements and higher yields. To date, to our knowledge, there is no report about the application of microwave irradiation for the Stetter reaction. As part of an ongoing program in our laboratory to synthesize a variety of flavonoid-like compounds under mild conditions, we herein report the first example of a microwave-assisted intramolecular Stetter reaction in RTILs.

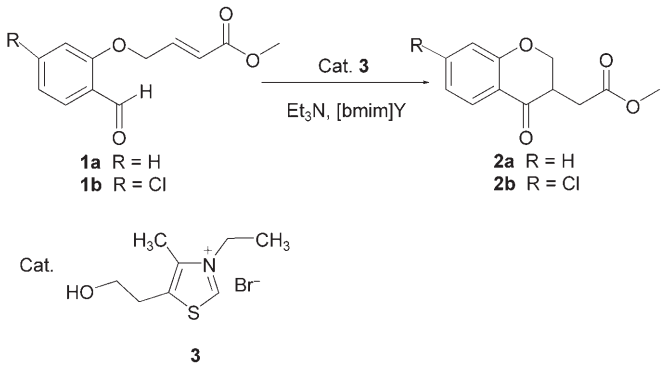
The substrates for the intramolecular Stetter reaction were easily prepared using the condensation reaction of salicyaldehydes with 4-halocrotonate esters ($E/Z \geqq 19:1$) according to the reported method.[9] The intramolecular Stetter reaction of (*E*)-methyl 4-(2-formylphenoxy)but-2-enoate was selected as a model to optimize the reaction conditions, using butylmethylimidazolium tetrafluoroborate $[bmim]^+ [BF_4]^-$ as the solvent (Scheme 2).

The commercially available and commonly used 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **3** was chosen as a catalyst and its concentration was optimized first (Table 1). Without catalyst the reaction afforded only a small amount (5%) of the product (Entry 1). Under this situation, the formation of **2a** was expected since it is known that salts of various heterocycles, including imidazolium salts, can also be used as catalysts. Therefore, the ionic liquids used as solvent is also able to function as a catalyst, even if it

Table 1. Optimization of the model reaction under microwave irradiation.

No.	Substrate	Solvent	Catalyst [%]	Temp. [°C]	Time [min]	Product	Yield [%][a]
1	**1a**	[bmim][BF_4]	0	80	20	**2a**	5
2	**1a**	[bmim][BF_4]	5	80	20	**2a**	55
3	**1a**	[bmim][BF_4]	10	80	20	**2a**	86
4	**1a**	[bmim][BF_4]	15	80	20	**2a**	96
5	**1a**	[bmim][BF_4]	20	80	20	**2a**	95
6	**1a**	[bmim][BF_4]	15	60	20	**2a**	81
7	**1a**	[bmim][BF_4]	15	100	20	**2a**	92
8	**1a**	[bmim][BF_4]	15	80	10	**2a**	85
9	**1a**	[bmim][PF_6]	15	80	20	**2a**	91
10	**1b**	[bmim][BF_4]	15	80	5	**2b**	98

[a] The yield was measured by HPLC.



Scheme 2.

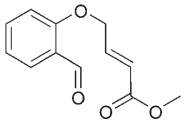
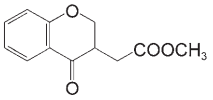
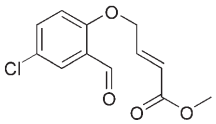
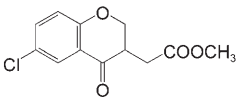
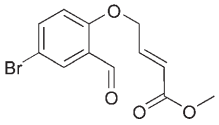
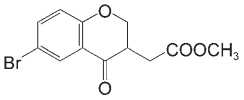
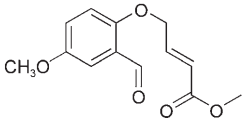
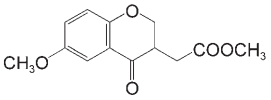
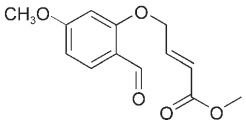
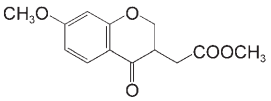
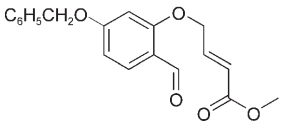
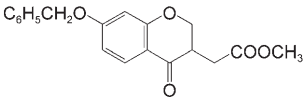
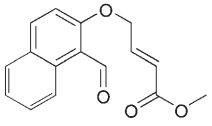
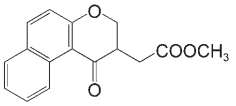
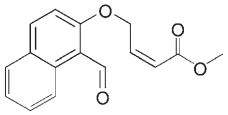
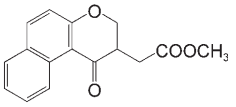
is less active than the usual thiazolium salts, and the yields of the desired product **2a** in that case are very poor. Subsequently, it was observed that when the quantity of thiazolium salt **3** increased from 5 to 15 mol%, the yield of **2a** improved accordingly to 96% (entries 2 to 4). The use of 20 mol% of catalyst did not give any further improvement in the yield of the product (entry 5). Therefore, we selected 15 mol% of catalyst for the next experiments. Varying the reaction temperature from 80°C to 60°C for the same irradiation time of 20 min decreased the yield of **2a** from 96% to 81% (entry 6). Raising the reaction temperature from 80°C to 100°C did not improve the yield of **2a** (entry 7). Shortening the irradiation time from 20 min to 10 min for the same reaction temperature (80°C) also decreased the yield of **2a** from 96% to 85% (entry 8). Then, we checked the influence of the nature of the ionic liquid on the reaction: changing the counter ion to $[PF_6]^-$ gave similar yields of **2a** (entry 9). It has been established by Grée's group[7] that using ionic liquid as solvent always gave moderate yields (<70%). However, it must be noted that not only significantly better yields were obtained by using microwave irradiation but also the reaction time was reduced from hours (10–34 h) under conventional heating to 20 min under microwave irradiation. Finally, it was shown that the same conditions could be applied with success to other substrates (entry 10).

Next, we studied the extension of these reaction conditions to other substrates (Table 2). In each case, the reaction proceeded smoothly to afford the desired products with good to excellent isolated yields (75–94%) in a very short time (5–20 min), while conventional heating in DMF solution gave isolated yields of 29–81% in 1.5 h. Although the ionic liquid under conventional heating gave moderate to good isolated yields of 45–88%, it always took a much longer time (2.5–10 h) to finish the reaction. In addition, substituents on the aromatic ring, such as Cl, Br, CH_3O, and $C_6H_5CH_2O$, have practically no obvious effect on the yield. However, the substrate bearing an NO_2 group on the benzene ring did not undergo any reaction under conventional conditions, but gave an abnormal product under microwave irradiation whose structure was assigned by ^{1}HNMR, MS and X-ray diffraction analysis (Figure 1) to be methyl 2-(2-methyl-5-nitro-3-oxo-2,3-dihydrobenzofuran-2-yl)acetate **4**. A plausible mechanism for the formation of **4** is outlined in Scheme 3. Due to the existence of the nitro group in the *para* position, the retro-Michael addition of **2i** was strongly facilitated to afford the putative intermediate **5a**,[10] which isomerized under basic conditions *via* a 1,3 H-shift to afford the electrophilic alkene **5b**. Then, **5b** took part in an intramolecular Michael addition to give compound **4**.

In addition, we also observed the effect of the Michael acceptor's olefin geometry. We were intrigued to find that the parent substrate **7** with the *E*-configuration cyclized in excellent isolated yield (85%, entry 7), however, only a trace of product was observed in the case of *Z*-isomer **8** under the same reaction conditions (entry 8).

It should be noted that one of the key aspects of the use of RTILs in organic synthesis is the possibility to recycle and reuse such solvents. At the end of the first run of the reaction, the products were extracted with ether and the ionic liquid solvent was reused directly

Table 2. Microwave-assisted intramolecular Stetter reaction using ionic liquid as solvent.

No.	Substrates	Products	DMF Yield [%][a]	Ionic Liquid[b] Time [h]	Ionic Liquid[b] Yield [%]	Ionic Liquid Under Microwave Time [min]	Ionic Liquid Under Microwave Yield [%][c]	Ionic Liquid Under Microwave Yield [%][d]	Ionic Liquid Under Microwave Yield [%][e]
1			65/60	5	85/80	20	96/91	90	88
2			85/81	2.5	92/88	5	98/94	93	92
3			71/69	2.5	79/75	5	81/75	79	72
4			69/65	8	79/74	20	89/84	87	84
5			72/67	8	78/74	20	88/83	84	81
6			74/70	9	83/78	15	89/89	87	83
7			32/29	10	51/45	20	95/85	91	88
8			trace	10	trace	20	trace	trace	trace

[a] Yields of the reaction using DMF as solvent. The left value was detected by HPLC, while the right value was the isolated yields. The reaction was carried out at room temperature.
[b] The reaction results under conventional condition using ionic liquid as solvent.
[c] Yields of the first cycle of ionic liquid solvent and the catalyst of thiazolium salts under microwave irradiation.
[d] HPLC yields of the second cycle of ionic liquid solvent and the catalyst of thiazolium salts.
[e] HPLC yields of the third cycle of ionic liquid solvent and the catalyst of thiazolium salts.

for a second run to give products with a slight decrease in the yield. A third cycle was also performed to give similar yield of products. Most importantly, after extraction, the thiazolium salts catalyst remains in the ionic liquid solvent and also can be reused.

In summary, we have developed an environmentally benign and highly efficient procedure for the preparation of chromanone derivatives *via* an intramolecular Stetter reaction. Under microwave irradiation, a variety of aromatic substrates undergo the intramolecular Stetter reaction in imidazolium-type RTILs as solvents, with thiazolium salts and Et_3N as catalysts. Under these conditions the reactions were finished in 5–20 min and the products could be isolated in good to excellent yields, usually higher than those obtained under conventional heating conditions. Furthermore, it was possible to recycle and reuse the ionic liquid and the catalyst thiazolium salts. To our knowledge, this is the first report about the application of microwave irradiation in the Stetter reaction. Efforts to develop an asymmetric Stetter reaction under microwave irradiation are now in progress.

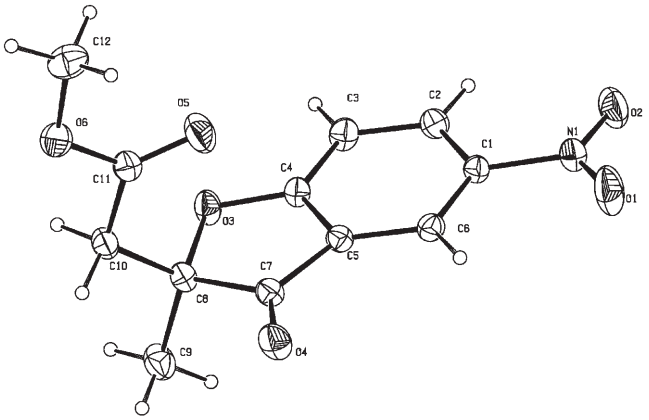


Figure 1. Crystal structure of 2-(2-methyl-5-nitro-3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (**4**).

Experimental Section

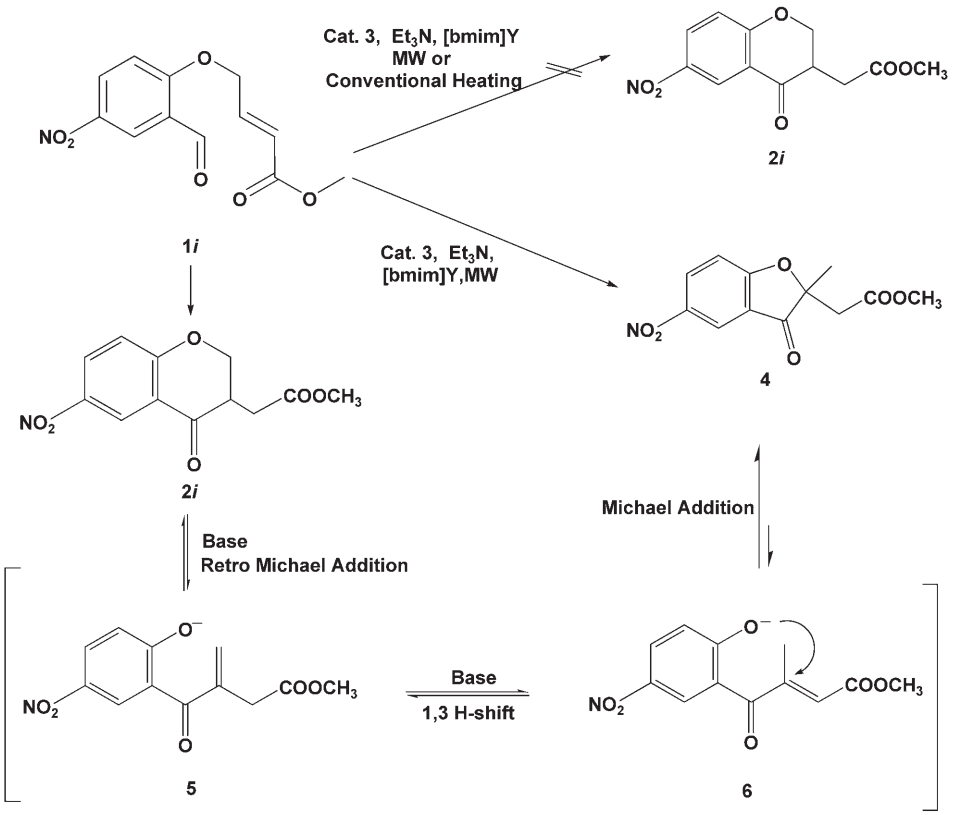
Melting points are uncorrected. Mass spectroscopy was performed on a Finnigan Trace mass spectrometer. NMR were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. HPLC were performed on an Agilent 1100 MWD instrument. Microwave irradiation reactions were carried out with a Smithsynthesizer™ instrument.

General Procedure for Microwave-Assisted Intramolecular Stetter Reaction in RTILs

Methyl 2-(3,4-dihydro-4-oxo-2*H*-chromen-3-yl) acetate as an example: In a microwave tube, Et_3N (0.20 g, 2 mmol) and methyl 4-(2-formylphenoxy)but-2-enoate **1a** (0.44 g, 2 mmol) were added into a suspension of 3-ethyl-5-(2-hydroxyethyl)-4- methylthiazolium bromide (76 mg, 15 mol%) in [bmim][BF_4]. Then, the sealed microwave tube was placed in the Smithsynthesizer™ and irradiated at 80 °C for 20 min. After completion of the reaction, the product was extracted with Et_2O (3×25 mL). The organic phase was dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO_2 to afford **2a**.

General Procedure for Intramolecular Stetter Reaction in RTILs under Conventional Heating

Methyl 2-(3,4-dihydro-4-oxo-2*H*-chromen-3-yl) acetate as an example: Et_3N (0.20 g, 2 mmol) and methyl 4-(2-formylphenoxy)but-2-enoate **1a** (0.44 g, 2 mmol) were added into a suspension of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (76 mg, 15 mol%) in [bmim][BF_4]. Then, the resulted mixture was heated at 80 °C for 2.5 h. After completion of the reaction, the product was extracted with Et_2O (3×25 mL). The organic phase was dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO_2 to afford **2a**.



Scheme 3. A plausible mecahnism for the formation of compound **4**.

General Procedure for Intramolecular Stetter Reaction Performed in DMF

Methyl 2-(3,4-dihydro-4-oxo-2*H*-chromen-3-yl) acetate as an example: A mixture of 1.54 g (7 mmol) of ester **1a**, 0.12 g (0.48 mmol) of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **3**, 0.4 mL (0.3 g, 3 mmol) of Et_3N, and 7 mL of DMF was stirred at room temperature for 1 h. After that, additional catalyst **3** (0.25 g, 1 mmol) and 0.8 mL (0.6 g, 6 mmol) of Et_3N were added. The resulted mixture was stirred for further 30 min. $CHCl_3$ (30 mL) and 10 mL of 10% aqueous HCl were added, the aqueous layer was extracted with 2×30 mL of $CHCl_3$. The combined extracts were washed with water, 5% aqueous $NaHCO_3$, and brine. The organic phase was dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO_2 to afford **2a**.

Preparation of Methyl 2-(2-Methyl-5-nitro-3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (4) under Microwave Irradiation in Room Temperature Ionic Liquids

To a suspension of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (76 mg, 15 mol%) in [bmim] $[BF_4]$ in a microwave tube were added Et_3N (0.20 g, 2 mmol) and 4-(2-formyl-4-nitrophenoxy)-but-2-enoic acid methyl ester (0.53 g, 2 mmol). The sealed tube was placed in the Smith-synthesizer™ and irradiated at 80 °C for 20 min. After completion of the reaction, the product was extracted with Et_2O (3×25 mL). The organic phase was dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO_2 to afford **4** in an isolated yield of 89%.

Determination of the X-Ray Crystal Structure of Compound 4

Crystal was grown by slowly evaportaing a solution of **4** in acetone. $C_{12}H_{11}NO_6$ ($Mr=265.22$), orthorhombic space group *Pbca*, $Z=8$, $a=6.4456(7)$ Å, $b=16.3915(17)$ Å, $c=23.353(3)$ Å, $\alpha=90°$, $\beta=90°$, $\gamma=90°$, $V=2467.3$ (5 Å ^{3}, Mo Kα radiation, $2.49° < \theta < 24.27°$, 13948 measured reflections, $T=292$ (2) K on a Brucker-Nonius kappa CCD. The structure was solved using direct methods (SHELXS97) and refined with SHELXK97 final R $[F^2 > 2\delta\ (F2)] = 0.0489$ and wR = $[w = 1/[\delta^2(F_o\ 2) + (0.0506P)^2 + 0.6292\ P]$ where $P = (F_o^2 + 2F_c^2)/3]$.

Acknowledgements

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