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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 431–434

Microwave-mediated solvent free Rap–Stoermer reaction for efficient synthesis of benzofurans

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Received 5 October 2006; revised 30 October 2006; accepted 10 November 2006
Available online 1 December 2006

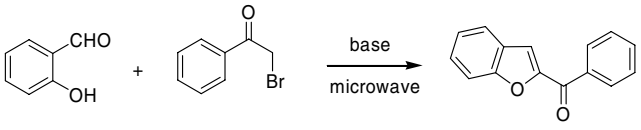
Abstract—The Rap–Stoermer reaction of salicylaldehydes with diverse phenacyl bromide and phenacyl iodides proceeded cleanly to afford various functionalized benzofurans in excellent yields under base-mediated solvent free microwave irradiation conditions.

Benzofurans are highly valuable molecular motifs often found in various natural products. Major interest associated with these molecules stems from their diverse range of pharmacological properties.[1,2] Despite the availability of multi-step methods for the synthesis of benzofurans,[2] a straightforward approach for their synthesis from easily available starting materials is always advantageous. The Rap–Stoermer reaction provides opportunity for the direct preparation of benzofurans via base-mediated reaction of salicylaldehydes with α-haloketones.[3a,b] The unique potential associated with the Rap–Stoermer reaction originates from its starting materials and hence a wide variety of substituted benzofurans can be easily synthesized depending on the functionality present in the salicylaldehyde and (or) α-haloketones. Unfortunately, the reported procedures involving solvent and heating conditions were not efficient giving lower yields in several cases.[3] Recently reported solid state studies on the Rap–Stoermer reaction provided valuable insights into the mechanistic details of this reaction.[3d]

The application of microwaves in organic synthesis is a widely accepted tool to achieve clean reaction conditions in the context of green and sustainable alternative methods.[4,5] In particular, reactions using solvent-free conditions would be more attractive to perform under microwave irradiation. So, to obviate the use of solvent and to perform the Rap–Stoermer reaction under clean conditions, we have studied this reaction under solvent-free microwave irradiation conditions for the efficient synthesis of benzofurans in short reaction times.

The Rap–Stoermer reaction was normally performed using alkaline base in alcoholic medium, which often produced poor to moderate yields of benzofuran products.[3a,b] In order to investigate this method under solvent free microwave conditions, we examined the efficiency of various bases on the reaction of salicylaldehyde with phenacyl bromide (Table 1).

Table 1. Screening of the reaction of salicylaldehyde with phenacyl bromide[a]



Entry	Base	MW (W)	Time (min)	Conv. (%)[b]
1	NaOAc	850	0.5	17
2	KOAc	850	0.5	15
3	Na_2CO_3	850	0.5	<1
4	K_2CO_3	850	0.5	89
5	K_3PO_4	850	0.5	97
6	K_3PO_4	850	0.25	85
7	K_3PO_4	600	0.5	54
8	K_3PO_4	600	1	85
9	K_3PO_4	600	1.5	93
10	K_3PO_4	600	2	95

[a] Conditions: salicylaldehyde (1 equiv), phenacyl bromide (1 equiv), base (2.2 equiv).
[b] Based on GC analysis.

Keywords: Benzofurans; Rap–Stoermer reaction; Microwave; Solvent free conditions.
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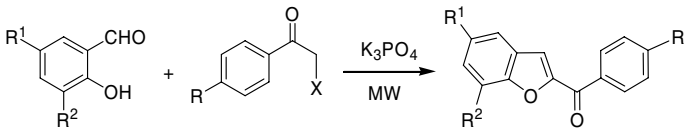
doi:10.1016/j.tetlet.2006.11.077

Table 2. Synthesis of benzofurans [a,b,c]



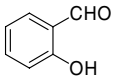
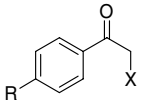
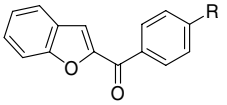
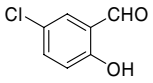
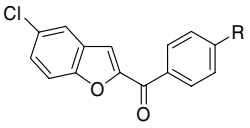
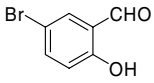
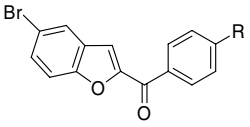
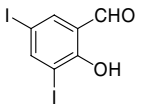
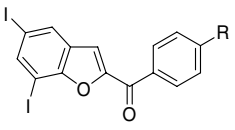
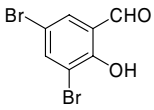
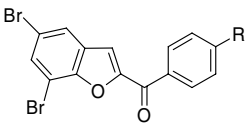
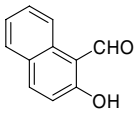
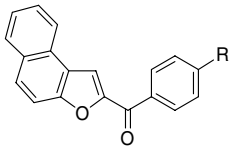
Entry	Salicylaldehyde	Phenacyl halide (equiv)	MW (W)	Time (min)	Benzofuran	Yield (%)
						
1		R = H (1.0); X = Br	600	2.0	R = H	93
2		R = Br (1.5); X = Br	850	2.0	R = Br	90
3		R = Br (1.0); X = Br	600	3.0	R = Br	91
4		R = Me (1.1); X = Br	600	2.5	R = Me	94
5		R = OMe (1.2); X = Br	600	1.5	R = OMe	93
6		R = H (1.2); X = I	600	1.0	R = H	93
7		R = Me (1.2); X = I	600	0.5	R = Me	91
						
8		R = H (1.1); X = Br	600	2.5	R = H	98
9		R = Br (1.5); X = Br	850	3.0	R = Br	93
10		R = Me (1.0); X = Br	600	2.0	R = Me	92
11		R = OMe (1.2); X = Br	600	1.5	R = OMe	92
12		R = H (1.2); X = I	600	1.0	R = H	93
13		R = Me (1.2); X = I	600	1.0	R = Me	90
14		R = OMe (1.2); X = I	600	1.5	R = OMe	92
						
15		R = H (1.1); X = Br	600	1.0	R = H	92
16		R = Br (1.0); X = Br	600	1.5	R = Br	91
17		R = Me (1.1); X = Br	600	1.0	R = Me	94
18		R = OMe (1.2); X = Br	600	2.0	R = OMe	95
19		R = H (1.2); X = I	600	0.5	R = H	93
20		R = Br (1.5); X = I	600	1.5	R = Br	88
21		R = Me (1.2); X = I	600	1.0	R = Me	87
22		R = OMe (1.5); X = I	600	2.0	R = OMe	78
						
23		R = H (1.1); X = Br	600	1.5	R = H	64
						
24		R = H (1.5); X = Br	850	0.5	R = H	74
25		R = Br (1.5); X = Br	850	2.0	R = Br	79
26		R = Me (1.5); X = Br	850	0.5	R = Me	78
27		R = OMe (1.5); X = Br	850	1.0	R = OMe	92

Table 2 (*continued*)

Entry	Salicylaldehyde	Phenacyl halide (equiv)	MW (W)	Time (min)	Benzofuran	Yield (%)
						
28		R = H (1.5); X = Br	600	0.5	R = H	90
29		R = Br (1.5); X = Br	850	2.0	R = Br	91
30		R = Me (1.2); X = Br	600	0.5	R = Me	92
31		R = OMe (1.2); X = Br	600	1.0	R = OMe	91
32		R = H (1.2); X = I	600	1.0	R = H	90
33		R = Br (1.5); X = I	600	3.0	R = Br	91
34		R = Me (1.2); X = I	600	0.5	R = Me	91
35		R = OMe (1.5); X = I	600	1.5	R = OMe	91

[a] In all cases K_3PO_4 (2.2 equiv) was used as the base.
[b] Isolated yields obtained after column chromatography. All the products were characterized by ^1H, ^{13}C NMR, IR and mass spectral analysis.
[c] A domestic microwave oven (Samsung M183DN, 2450 MHz) was used for irradiation.

In this study, sodium acetate, potassium acetate and sodium carbonate failed to deliver good conversions (entries 1–3) to benzofuran. Potassium phosphate and potassium carbonate were found to be efficient giving high conversions in short reaction times (entries 4 and 5). Further scrutiny with potassium phosphate as base and by varying the microwave power, it was found that the exposure time could be easily tuned without affecting the overall conversions (entries 6–10).

To expand the scope of this reaction, a variety of functionalized salicylaldehydes were employed along with electronically diverse phenacyl halides (bromides and iodides) and the results are summarized in Table 2. The reactivity of diverse salicylaldehydes with phenacyl bromides and iodides was found to be efficient affording the corresponding benzofurans in excellent yields. It is worth mentioning that the change of electronics in phenacylbromide and iodides did not affect the overall reactivity, and high yields of benzofurans were obtained. Despite being thermally labile, phenacyl iodides also reacted well under solvent free microwave conditions giving high yields of benzofurans. The excellent reactivity observed with various phenacyl iodides was almost similar to that observed with the corresponding phenacyl bromides. In addition, the reactivity of various mono and di-substituted salicylaldehydes was found to be efficient under the present conditions. Importantly, the various functionalized benzofurans that were obtained would be useful precursors for the synthesis of a variety of natural products possessing a benzofuran nucleus. In addition, the high yields of benzofuran obtained in very short reaction times are a reflection of the advantage and suitability associated with the Rap–Stoermer reaction under solvent free microwave irradiation.

In summary, a microwave-mediated solvent free Rap–Stoermer reaction has been reported for the synthesis of benzofurans from a variety of salicylaldehydes and phenacyl halides.[6] Some of the advantages and highlights of the present microwave protocol include, solvent free clean reaction conditions and high yields of benzofurans obtained in short reaction times. In addition, the 2-aroyl benzofurans formed using this method are also important as the corresponding carbinols (reduction products) are known to have hypolipidemic activity.[3b]

Acknowledgements

The authors thank CSIR, India, and IIT Kanpur for financial support. D.K.A. and D.B. thank UGC, India, and IIT Kanpur, respectively, for research fellowships.

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6. *Representative procedure:* In a typical experiment, a 15 mL open glass vial with a 20 mm diameter, was charged with salicylaldehye (0.122 g, 1 mmol), phenacyl bromide (0.199 g, 1 mmol) and potassium phosphate (0.467 g, 2.2 mmol). The mixture was stirred gently with a spatula for a few seconds and was subjected to domestic microwave irradiation (Samsung, M183DN, 2450 MHz) at 600 W for 2 min. After cooling, the crude solid mixture was quenched with 5% dilute HCl and extracted with ethyl acetate (2×15 mL). The organic extract was dried over $MgSO_4$ and concentrated. The crude product was subjected to column chromatography on silica gel using hexane–ethyl acetate as eluent and the pure benzofuran (0.206 g, 93%) was isolated. The product was characterized by ^{1}H, ^{13}C NMR, IR and mass spectral analysis.