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An Efficient and General Procedure for Room-Temperature Synthesis of Benzofurans under Solvent-Free Conditions Using KF/Al_2O_3

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Dedicated to Professor Dr. H. Firouzabadi on the occasions of his 65th birthday and retirement

Room temperature Rap-Stoermer condensation of α-haloacetophenone with various 2-hydroxyarylaldehydes mediated by KF/Al_2O_3 resulted in sole formation of good to excellent yields of various substituted benzofurans in the absence solvent or extra stimulant.

Keywords: Benzofuran, Rap-Stoermer reaction, KF/Al_2O_3, Solvent-free

INTRODUCTION

Benzofuran derivatives constitute highly valuable heterocyclic motifs found in the structure of many natural [1] and synthetic products [2]. Derivatives of these compounds are known to possess important pharmaceutical [3], antifungal [4], antitumor [5], and other bioorganic properties [6]. In addition, benzofurans are used in cosmetic formulations [7] and have the application as synthetic precursors for optical brighteners [8]. Many multi-step synthetic approaches for the construction of the benzofuran ring exist in which the key-step includes dehydrative annulation of phenols bearing appropriate ortho vinyllic substituents [9], intramolecular cyclization of substituted allyl-aryl ethers [10], cyclization of o-formylphenoxyacetic acids or esters [11], or ring-closure of arylacetylenes [12]. Perhaps, the most straightforward method for one-pot preparation of benzofuran derivatives is the Rap-Stoermer condensation of salicylaldehyde with α-haloketones [13] providing the opportunity for the synthesis of a diverse array of benzofuran derivatives in a single step process. The reaction is traditionally carried out under basic conditions in refluxing alcoholic solvents giving low yields of products in many occasions [3-4]. In line with the context of green and sustainable chemistry, several reports are recently released to expand the synthetic applicability of Rap-Stoermer reaction by using microwave irradiation [14], solvent-free systems [15], polymer-supported reagents [16], and solid state synthesis [17]. However, these reactions are still conducted at high temperature [15,16], require the use of commercially unavailable starting materials [17], conducted in refluxing solvents [16] or need an external stimulant to proceed [14,17].

In recent years, potassium fluoride on alumina (KF/Al_2O_3) [18] has emerged as an environmentally friendly and very powerful solid phase reagent for various organic functional manipulations such as ring closure reactions [19], epoxidation of alkenes [20], ether synthesis [21], amide [22] and amine [23] chemistry, Michael addition [24], aldol condensation [25], alkene synthesis [26], rearrangement processes [27], and cycloaddition reactions [28]. A number of advantages are associated with the use of this reagent like avoiding the

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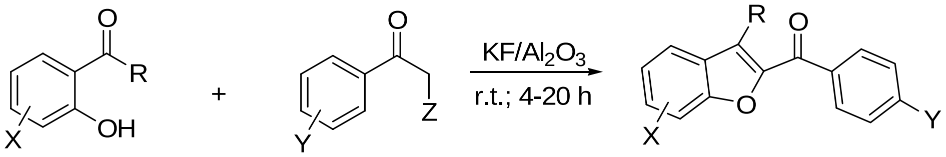


1a: R = H, X = H
1b: R = H, X = 3-OMe
1c: R = H, X = 4-NO_2
1d: R = H, X = 4-Br
1e: R = Me, X = H

2a: Y = H, Z = Cl
2b: Y = 4-Br, Z = Br
2c: Y = 4-OMe, Z = Br

3aa-3dc

Scheme 1

cleavage step required in many solid phase syntheses [29], decrease of solvent use, no special handling requirement, easy monitoring of reactions and convenient workup procedure by removal of the solid from the reaction mixture via a simple filtration. In continuation of our previous works on environmentally sustainable reactions [30], we would like to herein report a novel procedure for efficient Rap-Stoermer condensation of α-haloketones with various salicylaldehyde derivatives performed at room temperature in the presence of KF/Al_2O_3 under solvent-free conditions (Scheme 1).

EXPERIMENTAL

General: Reactions were monitored by TLC and GC. NMR spectra were obtained on a FT-NMR Bruker Ultra Shield^{TM} (500 MHz) or Bruker AC 80 MHz as $CDCl_3$ solutions and the chemical shifts were expressed as δ units with Me_4Si as the internal standard. GC experiments were carried out using a Fisons 8000 apparatus. All chemicals and reagents were purchased from commercial sources.

Preparation of KF/alumina [31]: To a stirred solution of potassium fluoride (20g) in water (150 ml) is added neutral alumina (60-80 mesh, 30 g) in water (150 ml). After 30 minutes, the water is evaporated in a rotary evaporator at ~60 ˚C. When most of the water has been removed, the remaining mixture is heated to 140-150 ˚C and maintained at that temperature under vacuum (5 mmHg) for 6h to give 50 g of KF-alumina reagent.

Typical procedure for KF/Al_2O_3 mediated Rap-Stoermer condensations: An equimolar mixture of **1** (5 mmol) and **2** (5.5 mmol) was suspended in 5 gr KF/Al_2O_3 and the mixture was stirred at room temperature until TLC and GC experiments showed complete disappearance of the starting materials. The mixture was extracted with Et_2O (2X30 mL), the extracts were combined, and the volatile portion was removed under reduced pressure. The product was purified with short column chromatography over silica gel using *n*-hexane/EtOAc (7:1). The spectroscopic and physical properties of the products were obtained and compared with those available in the literature [2e,14,32].

Spectral data for new compounds

(4-Bromophenyl)(7-methoxybenzofuran-2-yl)methanone (**3bb**). Yellow crystals were obtained in 98% yield, mp 93–95 ^oC; IR (KBr, cm^{-1}) 1639, 1554, 1280, 871; ^1H NMR ($CDCl_3$) δ 4.08 (s, 3H), 7.02 (d, 1H, *J* = 7.8 Hz), 7.30 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.61 (s, 1H), 7.74 (d, 2H, *J* = 8.41 Hz), 8.03 (d, 2H, *J* = 8.41 Hz); ^{13}C NMR ($CDCl_3$) δ 56.5, 110.1, 115.4, 116.7, 125.2, 128.5, 128.9, 131.6, 132.3, 136.1, 146.2, 146.5, 152.9, 183.1; MS (70 eV) m/z (%): 332, 330 (M^+), 251, 175, 76. Calcd. For $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35. Found: C, 58.01; H, 3.47.

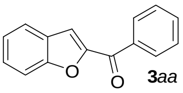
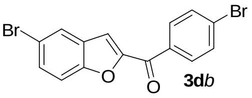
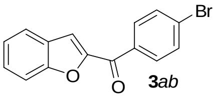
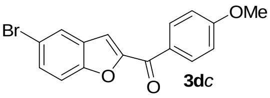
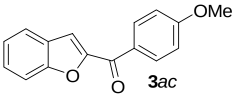
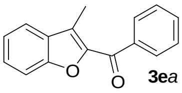
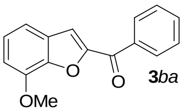
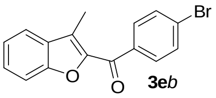
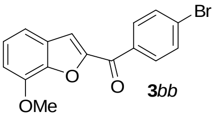
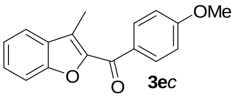
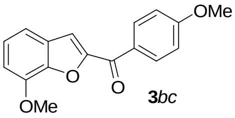
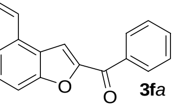
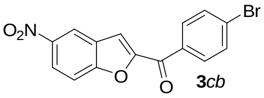
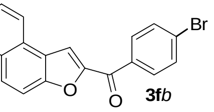
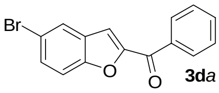
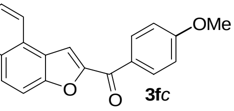
(7-Methoxybenzofuran-2-yl)(4-methoxyphenyl)methanone (**3bc**). White crystals were obtained in 97% yield, mp 66–68 ^oC; IR (KBr, cm^{-1}) 1664, 1593, 1315, 1230, 1160; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H), 4.07 (s, 3H), 6.98 (d, 1H, *J* = 7.7 Hz), 7.05 (d, 2H, *J* = 8.8Hz), 7.26 (dd, 1H, *J* = 7.8, 7.9 Hz), 7.32 (d, 1H, *J* = 7.8), 7.56 (s, 1H), 8.19 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 55.9, 56.5, 109.8, 114.3, 115.3, 115.8, 125.0, 129.1, 130.2, 132.5, 145.9, 146.5, 153.6, 164.0, 182.8; MS (70 eV) m/z (%): 282 (M^+), 252, 135. Calcd. For $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.15; H, 5.12.

(4-Bromophenyl)(3-methylbenzofuran-2-yl)methanone (**3eb**). White crystals were obtained in 78% yield, mp 103–105 ^{o}C; IR (KBr, cm^{-1}) 1643, 1562, 1296, 929; ^{1}H NMR ($CDCl_3$) δ 2.71 (s, 3H), 7.39 (d, 1H, *J* = 6.8, 7.8 Hz), 7.59-7.53 (m, 2H), 7.71 (d, 2H, *J* = 8.5 Hz), 7.75 (d, 1H, *J* = 7.8 Hz), 8.03 (d, 2H, *J* = 8.47 Hz),; ^{13}C NMR ($CDCl_3$) δ 10.5, 112.7, 122.0, 123.9, 128.0, 128.2, 128.9, 129.6, 131.8, 132.1, 136.9, 148.4, 154.7, 185.0; MS (70 eV) m/z (%): 315, 314 (M^{+}), 235, 207. Calcd. For $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52. Found: C, 60.59; H, 3.55.

RESULTS AND DISCUSSION

The reaction between α-chloroacetophenone with salicylaldehyde was investigated under various sets of conditions to find the optimum conditions. A solvent-free suspension of the two reactants and KF/Al_2O_3 led to 98% formation of product **3aa** within 4 hours time period (Table 1, entry 1). Conduction of the same reaction in the absence of KF/Al_2O_3 led to formation of no product after several days

Table 1. KF/Al_2O_3 mediated Rap-Stoermer condensations.

Entry	Substrates	Product	%Yield/Time (h)	Entry	Substrates	Product	%Yield/Time (h)
1	**1*a*** + **2*a***	 **3*aa***	98/4	9	**1*d*** + **2*b***	 **3d*b***	95/6
2	**1*a*** + **2*b***	 **3*ab***	98/6	10	**1d** + **2*c***	 **3d*c***	96/6
3	**1*a*** + **2*c***	 **3*ac***	96/6	11	**1e** + **2*a***	 **3e*a***	75/20
4	**1*b*** + **2a**	 **3*ba***	9064	12	**1e** + **2*b***	 **3e*b***	78/20
5	**1*b*** + **2*b***	 **3*bb***	98/6	13	**1e** + **2*c***	 **3e*c***	93/20
6	**1*b*** + **2*c***	 **3*bc***	97/6	14	**2*a*** + 2-hydroxy- 1-naphthaldehyde	 **3f*a***	81/4
7	**1*c*** + **2*b***	 **3*cb***	93/20	15	**2*b*** + 2-hydroxy- 1-naphthaldehyde	 **3f*b***	95/4
8	**1*d*** + **2a**	 **3d*a***	92/6	16	**2*c*** + 2-hydroxy- 1-naphthaldehyde	 **3f*c***	92/4

^{a}Isolated yields

room-temperature mixing, illustrating the promoting effect of the solid catalyst. The product was easily obtained in high purity by a simple diethyl ether extraction. The optimized conditions were employed to investigate the Rap-Stoermer condensation of salicylaldehyde with other substrates bearing electron-withdrawing and electron-releasing groups. Therefore, reactions of **1a** with **2b** (entry 2) and with **2c** (entry 3) gave 98 and 96% of **3ab** and **3ac**, respectively. The generality of the procedure was shown by subjecting derivatives of o-hydroxybenzaldehydes to undergo condensation with different α-haloacetophenones (entries 4-10). Furthermore, o-hydroxyacetophenone (entries 11-13) and 2-hydroxy-1- naphthaldehyde (entries 14-16) conveniently exhibited similar reactions. In all cases, reactions smoothly reached to completion within 4-20 hours time periods and more than 81% of the desired products were isolated by simple ethereal extraction.

In summary, we have developed a novel and general procedure for room-temperature Rap-Stoermer condensation of α-haloacetophenone with various 2-hydroxyarylaldehydes mediated by KF/Al_2O_3. Reactions complete in short time periods in the presence of no solvent or external stimulant and the procedure is applicable to both 2-hydroxyacetophenone and 2-hydroxyarylaldehydes. The versatility of the reaction, production of pure single compounds, and easy procedure and work up are among other benefits of the present method.

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