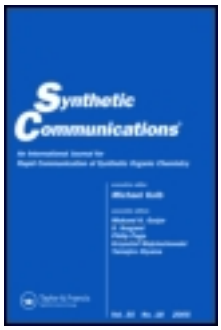

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Synthesis of β-Aryl-β-sulfanyl Ketones by a Sequential One-Pot Reaction Using KF/Al_2O_3 in Glycerol

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SYNTHESIS OF β-ARYL-β-SULFANYL KETONES BY A SEQUENTIAL ONE-POT REACTION USING KF/Al_2O_3 IN GLYCEROL

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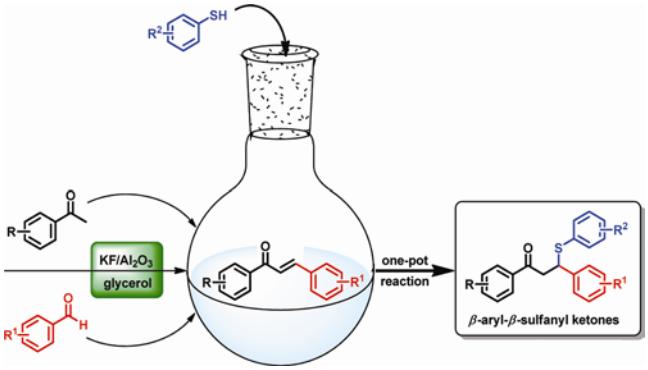
Abstract

The title compounds were synthesized by a sequential one-pot reaction of aryl aldehydes, aryl-methyl ketones and thiols promoted by KF/Al2O3. This methodology affords a large number of ?-aryl-?-sulfanyl ketone derivatives from aliphatic and aromatic thiols in good yields and is applicable also for solid substrates.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



Keywords: sulfanyl ketones, Glycerol, one-pot reaction, KF/Al2O3, green chemistry

INTRODUCTION

Conjugate addition reactions of sulfur nucleophiles to electron-deficient olefins are one of the most important synthetic tools for the generation of carbon-sulfur bonds. Organosulfur groups are valuable intermediates in organic synthesis[1] and this structural unit is frequently present in naturally occurring and biologically active compounds.[2] Particularly, the synthetic utility of *β*-sulfanyl ketones has been demonstrated in the syntheses of naturally occurring spiroketal pheromones,[3] alkene protective group,[4] and as versatile homoenolate equivalents.[5] More recently, these functionalized ketones were found to have ant iproliferative activity of breast cancer cell lines (Figure 1).[6] Thus, the development of efficient and new methodologies for synthesizing this class of compounds has been emerged in organic synthesis.

Traditional methods for the formation of C-S bonds via thia-Michael addition commonly make use of the already available *α*,*β*-unsaturated ketones. The 1,4-addition of thiols can be catalyzed by alkali metal alkoxides[7] or Lewis acids.[8] Solid catalysts, such as acid adsorbed on silica gel,[9] zeolites,[10] natural and synthetic phosphates,[11] montmorillonite clays,[12] neutral alumina[13] and base supported on alumina[14] have been used to perform the 1,4-addition of thiols to a series of electron-poor alkenes. Besides, the use of non-volatile and non-toxic solvents, such as water[15] and ionic liquids[16] to perform the Michael addition was also described. To the best of our knowledge, there are only a few methods to obtained *β*-aryl-*β*-sulfanyl ketones by direct one-pot Claisen-Schmidt condensation of aryl aldehydes with acetophenones and subsequent addition of thiols.[17] Besides scarce, these methods have some disadvantages, such as, cumbersome workup, low substrate scope and yield and, in some cases, they are not suitable to solid substrates.

Therefore, the development of efficient and practical methods for the synthesis of *β*-sulfanyl ketones is attractive.

On the other hand, in recent years glycerol has emerged as a eco-friendly and secure solvent for organic reactions,[18] including Pd-catalyzed Heck and Suzuki cross-couplings, Cu-catalyzed cross-coupling of diaryl diselenides with aryl boronic acids, base- and acid-promoted condensations, catalytic hydrogenation and asymmetrical reduction.[19] The low toxicity, biodegradability, high boiling point and polarity, and ready availability from biomass are some of the peculiar properties of glycerol.[20] More recently, the electrophilic activation of carbonyl compounds in glycerol-promoted reactions, allowing the elimination of the use of acidic catalysts was demonstrated.[21]

Because our interest in new uses for glycerol, and in continuation on our studies toward the development of new and cleaner methods for the synthesis of organochalcogenium compounds, we present here a sequential, one-pot procedure for the synthesis of *β*-sulfanyl ketones using glycerol as solvent and KF/alumina as catalytic system (Scheme 1).

RESULTS AND DISCUSSION

Our initial studies were focused on the development of an optimum set of reaction conditions to afford the intermediate chalcone **3a** (Table 1). Initially, we reacted acetophenone **1a** (1.0 mmol) with benzaldehyde **2a** (1.0 mmol) using KF/Al_2O_3 50% (0.07g) as base system in glycerol (5.0 mL) at room temperature. Under these conditions,

no product was observed. To our satisfaction, increasing the temperature to 90 °C, the reaction proceeds smoothly and the desired product **3a** was obtained in 78% yield (Table 1, entry 3). In another experiment, it was observed that using 1.2 mmol of **2a**, the product **3a** was obtained in 90% yield (Table 1, entry 4). When others solvents were used, such as PEG-400, ethanol, THF and DMF, moderated to good yields of **3a** were obtained (Table 1; entries 5-8).

The influence of the amount of thiol **4a** was the next variable studied, aiming to obtain via one pot procedure the 1,3-diphenyl-3-(phenylsulfanyl)propan-1-one **5a** (Scheme 1). We observed that the use of 1.0 or 1.5 mmol of benzenethiol **4a** gives the desired product **5a** in moderated yield (Table 1, entries 9 and 10). Fortunately, when the amount of thiol **4a** was increased to 2.0 mmol, **5a** was obtained in 78% yield (Table 1, entry 11).

In an optimized reaction, a mixture of acetophenone **1a** (1.0 mmol), benzaldehyde **2a** (1.2 mmol) and KF/Al_2O_3 50% (0,07g) in glycerol (5.0 mL) was stirred for 4 h at 90 °C under N_2 atmosphere. After that, benzenethiol **4a** (2.0 mmol) was added and the stirring was maintained for additional 3 h.

Using these reaction conditions, 1,3-diphenyl-3-(phenylsulfanyl)propan-1-one **5a** was obtained in 78% yield. The possibility of reuse of the KF/Al_2O_3/glycerol system was also investigated. For this pourpose, after the time indicated in Table 1, the reaction was extracted with a mixture of hexane/AcOEt 95:5 (3× 2.0 mL) and the remaining glycerol phase was directly reused in a new reaction. Unfortunately, it was observed an

incomplete consume of starting acetophenone and benzaldehyde, giving only 45% yield of the intermediate chalcone **3a**.

To extend the scope of our methodology, the possibility of performing the reaction with other aryl-methyl ketones, aryl aldehydes and thiols was investigated and, in most cases, the reaction proceeded smoothly to give the respective *β*-aryl-*β*-sulfanyl ketones **5b-j** in good yields.

It was observed that the presence of electron-withdrawing and electron-donating groups in the aryl thiols caused a slightly decrease in the yield of *β*-sulfanyl ketones **5** (Table 2, entries 2-5). Thus, when *p*-chloro and *p*-bromo benzenethiol were added to the previous formed chalcone **3a**, the respective *β*-phenyl-*β*-(4-halophenylthio) ketones **5c** and **5d** were obtained after 7 h in 60 and 63% yield respectively (entries 3 and 4), while *o*-chloro benzenethiol **4e** gave **5e** in a similar yield after 8 h (Table 2, entry 5). The presence of electron-donating group adversely affect the reaction time, being necessary 14 h to obtain the functionalized ketone **5b**, derived from *p*-methoxy benzenethiol **4b** (Table 2, entry 2). In contrast, no apparent effect was observed when substituted ketones **1b-c** and anisaldehyde **2b** were used (Table 2, entries 8-10). Good results were obtained also using dodecanethiol **4f**, which reacted smoothly to afford **5f** in 64% yield after 7 h (Table 2, entry 6).

To our satisfaction, through of our methodology it is possible to obtain the final products starting from both, liquid and solid substrates. Thus, for example, the reaction of

acetophenone **1a**, benzaldehyde **2a** and *β*-naphthyl mercaptan **4g** furnished the desired product **5g** exclusively in 57% yield after 14 h (Table 2, entry 7).

In summary, a sequential one-pot reaction of aryl aldehydes, aryl-methyl ketones and thiols to synthesize *β*-aryl-*β*-sulfanyl ketones using KF/Al_2O_3 was developed. A range of substituted *β*-sulfanyl ketones was obtained in good yields starting from solid and liquid reagents and using glycerol as a green, environmentally friend solvent.

EXPERIMENTAL

General Remarks

The reactions were monitored by TLC carried out on Merck silica gel (60 F_{254}) by using UV light as visualizant agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. The ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded with a 500 MHz spectrometer (Bruker DRX), as noted. Chemical shifts are expressed as parts per million (ppm) downfield from tetramethylsilane as an internal standard. Coupling constants (*J*) are reported in Hertz. Low Resolution Mass Spectra (LRMS, EI) were measured on a Shimadzu GCMS-QP2010-Plus mass spectrometer. High-Resolution Mass Spectra: HR-ESI-MS were obtained on a LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific).

General Procedure For The Directly Synthesis Of *β*-Aryl-*β*-Sulfanyl Ketones[22]

To a round-bottomed flask containing the aryl-methyl ketone **1a** (0.120 g, 1.0 mmol), benzaldehyde **2a** (0.127 g, 1.2 mmol) and KF/Al_2O_3 50% (0.07 g), was added glycerol

(5.0 mL). The reaction mixture was allowed to stir at 90 °C for 4 hours under N_2 atmosphere. After that, it was added the thiol **4d** (0.376, 2.0 mmol) and the reaction progress was followed by TLC. After the time indicated in Table 2, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with water (3x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent, yielding 1,3-diphenyl-3-(4-bromophenylsulfanyl)propan-1-one **5d** (0.249 g, 63%). Yellow solid, mp 106-107 °C; IR (ν_{max}, cm^{-1}): 1674 (C=O). ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.2 Hz, 2H); 7.54 (t, J = 7.4 Hz, 1H); 7.42 (t, J = 7.6 Hz, 2H); 7.31-7.33 (m, 2H); 7.25 (t, J = 7.6 Hz, 2H); 7.17-7.20 (m, 1H); 7.14 (d, J = 8.6 Hz, 2H); 4.92 (dd, J = 7.8 and 6.6 Hz, 1H); 3.62 (dd, J = 17.2 and 7.8 Hz, 1H); 3.56 (dd, J = 17.2 and 6.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$); δ (ppm): 196.6, 140.9, 136.6, 134.2, 133.3, 133.2, 131.9, 128.6, 128.5, 128.0, 127.7, 127.5, 121.8, 48.3, 44.5. MS (relative intensity) *m/z*: 396 (2), 207 (9), 105 (100), 77 (26). HRMS (ESI): *m/z* calcd. for $C_{21}H_{17}BrOS$ $[M + H]^+$: 397.0262; found: 397.0266.

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22. Supporting Information: Full experimental detail ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

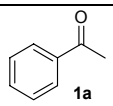
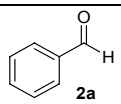
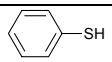
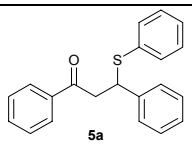
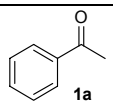
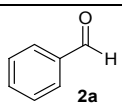
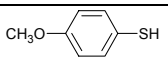
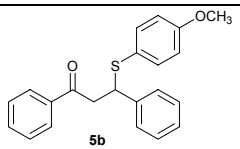
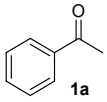
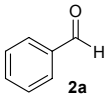
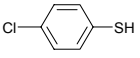
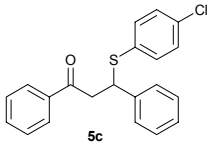
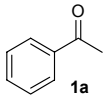
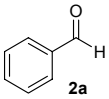
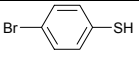
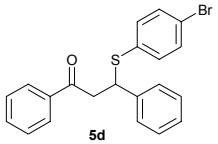
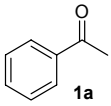
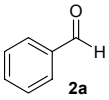
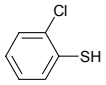
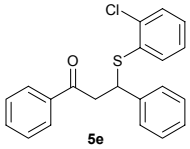
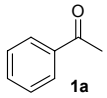
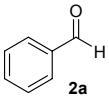
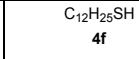
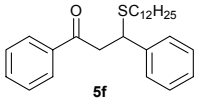
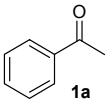
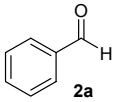
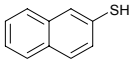
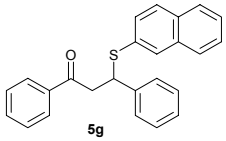
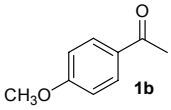
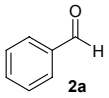
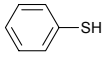
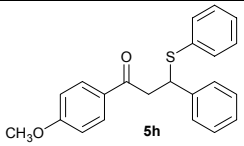
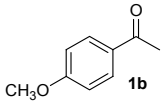
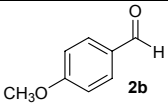
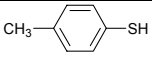
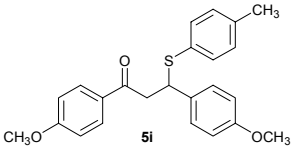
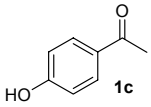
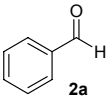
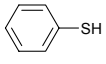
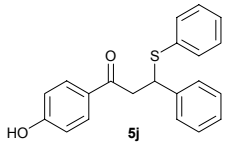
Table 1. Optimization in the syntheses of chalcone **3a** and *β*-phenyl-*β*-sulfanyl ketone **5a**[a]

Entry	**2a** (mmol)	**4a** (mmol)	Solvent	Temperature (^{o}C)	Product (Yield, %)[b]
1	1.0	-	glycerol	50	**3a** (42)
2	1.0	-	glycerol	75	**3a** (53)
3	1.0	-	glycerol	90	**3a** (78)
4	1.2	-	glycerol	90	**3a** (90)
5	1.2	-	PEG-400	90	**3a** (70)
6	1.2	-	ethanol	reflux	**3a** (60)
7	1.2	-	THF	reflux	**3a** (30)
8	1.2	-	DMF	90	**3a** (61)
9	1.2	1.0	glycerol	90	**5a** (59)
10	1.2	1.5	glycerol	90	**5a** (65)
11	1.2	2.0	glycerol	90	**5a** (78)

[a]Reactions performed in the presence of **1a** (1.0 mmol), **2a**, KF/Al_2O_3 (0.07 g), and solvent (5.0 mL) under N_2 atmosphere for 4 h to obtain **3a** and additional 3 h to **5a**.

[b]Yields are given for isolated product **3a** or **5a**.

Table 2. Scope and generality of the synthesis of the *β*-aryl-*β*-sulfanyl ketones **5a-j**.

Entry	Aryl-Methyl Ketone **1**	Aldehyde **2**	Thiol **4**	Product **5**	Time (h)	Yield (%)[a]
1	 **1a**	 **2a**	 **4a**	 **5a**	3	78
2	 **1a**	 **2a**	 **4b**	 **5b**	10	65
3	 **1a**	 **2a**	 **4c**	 **5c**	3	60
4	 **1a**	 **2a**	 **4d**	 **5d**	3	63
5	 **1a**	 **2a**	 **4e**	 **5e**	5	60
6	 **1a**	 **2a**	 **4f**	 **5f**	3	64
7	 **1a**	 **2a**	 **4g**	 **5g**	10	57
8	 **1b**	 **2a**	 **4a**	 **5h**	3	61
9	 **1b**	 **2b**	 **4h**	 **5i**	7	55
10	 **1c**	 **2a**	 **4a**	 **5j**	12	57

[a]Reactions performed in the presence of **1** (1.0 mmol), **2**, KF/Al_2O_3 (0.07 g), and solvent (5.0 mL) under N_2 atmosphere for 4 h to obtain **3**.

[b]Yields are given for isolated products.

Scheme 1.

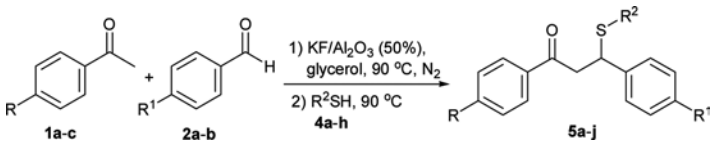


Figure 1. Drugs containing β-sulfanyl ketone unit in their structure