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ORIGINAL PAPER

Reaction of ammonium ylides with alkyl thiocyanates in aqueous and non-aqueous media

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Abstract Reaction of ammonium ylides with alkyl thiocyanates in aqueous and non-aqueous media is described. The reaction leads to alkyl thio-substituted acetophenones via addition of ammonium ylides to alkyl thiocyanates in organic solvents or in situ generated thiolate anions in aqueous media.

Keywords α-Sulfenylated ketones · Ylide · Alkyl thiocyanate · Water

Introduction

α-Sulfenylated ketones are versatile intermediates in organic synthesis [1, 2]. They have been used for 1,2-carbonyl transpositions [3] and preparation of α,β-unsaturated ketones [4], 1,2-diketones [5, 6], oxirans [7–9] and α-oxoacetals [10]. They also have been utilized for mono- and dialkylation of ketones [11] and functionalization of furans [12]. β-Hydroxy sulfides, which can be readily prepared from α-sulfenylated ketones, are common structural components in a vast group of natural products along with having useful biological and pharmaceutical activities [13–15].

The classic approach to the introduction of sulfur α to the carbonyl group involves the displacement of a halogen by a thiolate [16]. Direct sulfenylation of ketones using arylthiocyanate [17], arenesulfenyl acetate [18], aryl thiotoluenesulfonate [19] and arenesulfenyl chlorides [20] has also been reported. The most common method for α-sulfenylation of ketones involves the reaction of enolates with various sulfenylating reagents such as diphenyl disulfide, dimethyl disulfide, methyl methanethiosulfate, benzenesulfenyl chloride, *N*-(phenylthio)phthalimide and *N*-phenylthiocaprolactam [21–26]. These methods suffer from different disadvantages, such as unsatisfactory yields, entailing undesirable side reactions, multiple sequences required for the preparation of the substrate thiol and problems with the stability of the initial β-ketosulfides to the reaction conditions. The thiols, in particular those with low molecular weight, are odorous, harmful, highly volatile, and flammable, which can create serious environmental and safety problems. As a result, development of new methods to synthesize these classes of compounds is of considerable importance. Due to the environmental acceptance, abundance and low cost of water, organic reactions in water have received increased attention [27–32]. Ylide research has been developed in recent years, and ylides have now become powerful and versatile synthetic tools in organic chemistry [33–36].

Results and discussion

As part of our current studies on the reaction of ammonium ylides with different electrophiles [37–39], in this work we described the reaction of ammonium ylides with alkyl thiocyanates. In this procedure ammonium ylides are formed via the reaction of 2-bromo-1-aryl-1-ethanone and DABCO, which then react with alkyl thiocyanates in the presence of a base. This reaction, which proceeds in organic solvents and in water, forms β-ketosulfides in varying yields depending on the conditions employed. The results are shown in Table 1.

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Table 1 Optimization of reaction conditions of bromoacetophenone with DABCO and ethyl thiocyanate

Solvent	Base	*t* (h)	Yield (%)
CH_3CN	K_2CO_3	15	37
CH_3CN	Et_3N	15	25
CH_3CN	NaOH	15	32
CH_2Cl_2	K_2CO_3	15	<5
Benzene	K_2CO_3	15	<5
THF	NaOH	15	<5
H_2O	K_2CO_3	15	55
H_2O	NaOH	15	51

Table 2 Reaction of ammonium ylides and alkyl thiocyanates

Substrate	R	R′	Product	Yield (%)	Refs.
1a	Ph	CH_3	**2a**	53	[37–40]
1b	Ph	CH_3CH_2	**2b**	55	[39, 41–44]
1c	Ph	$PhCH_2$	**2c**	53	[39, 45–48]
1d	*p*-CH_3O-Ph	CH_3	**2d**	54	[40, 49, 50]
1e	*p*-CH_3O-Ph	CH_3CH_2	**2e**	61	[51, 52]
1f	*p*-Br-Ph	CH_3	**2f**	56	[49, 53]
1g	*p*-Br-Ph	CH_3CH_2	**2g**	55	[52]
1h	*p*-Ph-Ph	CH_3	**2h**	50	[54]
1i	*p*-Ph-Ph	CH_3CH_2	**2i**	49	

Even though it may not be the best method for the synthesis of alkyl thio-substituted acetophenones, it shows the unusual behavior of alkyl thiocyanates in reaction with ammonium ylides. As is shown in Table 1, the reaction using H_2O as the solvent and K_2CO_3 as the base gave the best results. The use of these optimal conditions for the reactions of different 2-bromo-1-aryl-1-ethanone and thiocyanate derivatives afforded good yields of 2-(alkylsulfanyl)-1-aryl-1-ethanones (Table 2).

The structures of all the synthesized compounds were established on the basis of their spectroscopic data and by comparison to published data in references given in Table 2.

A mechanistic rationalization for the reaction is provided in Scheme 1. In an organic solvent, deprotonation of quarternary ammonium salt **3** with the base forms the ylide **4**, which attacks the C≡N triple bond of the alkyl thiocyanate to yield the intermediate **5**. The intermediate **5** undergoes 1,2-alkyl thio-shift accompanied with DABCO elimination and leads to nitrile **6**. Hydrolysis of nitrile **6**, under the reaction conditions, affords *β*-keto acid **7**, which delivers the *β*-keto sulfide **2** via decarboxylation (Scheme 1).

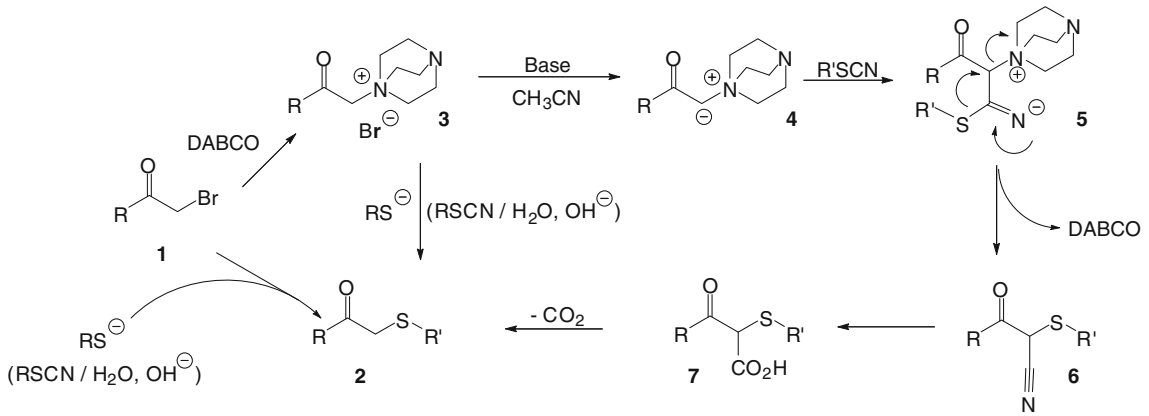
It is reasonable to accept that under the basic aqueous environment the alkyl thiocyanate is attacked by base, liberating the alkyl thiolate, and the thiolate displaces the DABCO in a nucleophilic substitution reaction.

In summary, reaction of ammonium ylides, derived from 2-bromo-1-aryl-1-ethanone and DABCO, with alkyl thiocyanates has been investigated in aqueous and non-aqueous media. The reaction leads to 2-alkyl thioacetophenones in a one-pot procedure. The notable advantages offered by this method are simple operation, environment-friendly reaction conditions and usage of alkyl thiocyanates as the thiolate source.

Experimental

*Typical procedure for the preparation of 2-(methylthio)acetophenone (**2a**)*

2-Bromoacetophenone (0.34 g, 1.73 mmol) and 0.19 g DABCO (1.73 mmol) were taken up in 10 cm^3 water, and



Scheme 1

the mixture was stirred at r.t. for 7 h. To this mixture 0.40 g K_2CO_3 (2.90 mmol) was added, and after 30 min 0.10 g methyl thiocyanate (1.15 mmol) was added and allowed to stir at reflux for 8 h. The reaction solution was extracted with dichloromethane. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude oil was purified by passing through a column of silica gel, eluting with 10 % EtOAc in *n*-hexane to afford **2a** as yellow oil (53 %); b.p.: 110 °C.

p-Methoxy-2-(methylthio)acetophenone (**2d**)
Yellow liquid (54%); b.p.: 175 °C.

p-Bromo-2-(ethylthio)acetophenone (**2g**)
Yellow crystals (55%); m.p.: 145–150 °C.

2-(Ethylthio)-p-phenylacetophenone (**2i**, $C_{16}H_{16}OS$)
Light yellow crystals (49%); m.p.: 67-69 °C; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.33$ (t, $J = 7.4$ Hz, 3H), 2.66 (q, $J = 7.4$ Hz, 2H), 3.87 (s, 2H), 7.45 (m, 1H), 7.52 (t, $J = 7.3$ Hz, 2H), 7.67 (d, $J = 7.0$ Hz, 2H), 7.74 (d, $J = 8.3$ Hz, 2H), 8.10 (d, $J = 8.3$ Hz, 2H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.6$, 26.8, 37.2, 127.71, 127.74, 128.7, 129.4, 129.8, 134.4, 140.3, 146.5, 194.6 ppm; IR (KBr): $\bar{\nu} = 2{,}956$, 1,672, 1,267, 1,122, 1,039, 740 cm^{-1}; MS: $m/z = 256$ (M^+, 5), 223 (23), 196 (79), 181 (100), 152 (97), 127 (13), 83 (19).

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