Addition of Thiocyanic Acid to Chalcones: Practical Synthesis of 1,3-Diaryl-3-isothiocyanatopropan-1-ones

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Abstract

Practical synthesis of 1,3-diaryl-substituted 3-isothiocyanatopropan-1-ones based on the reaction of chalcones with thiocyanic acid generated in situ by treatment of thiocyanate ammonium with dilute sulfuric acid has been developed.

Keywords

Chalcones; Isothiocyanates; Ketones; Thiocyanic acid; Addition

Introduction

β-Isothiocyanato aldehydes and ketones **1** (Fig. 1) with two highly reactive functional groups are valuable starting materials for the synthesis of a large number of nitrogen-containing acyclic and heterocyclic compounds.

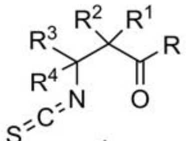

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Figure 1. General formula of β-isothiocyanato aldehydes and ketones **1**.

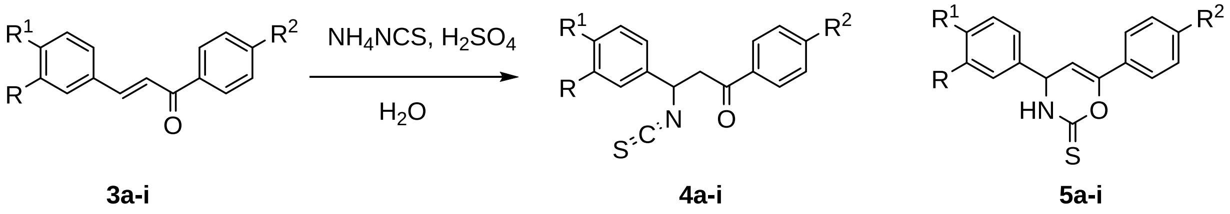
The first representatives of **1** were described in 1946.[1] Since then these compounds have been the focus of considerable attention.[2] Isothiocyanates **1** were used in synthesis of pyrimidines,[3] 1,3-oxazines,[4] 1,3-thiazines,[5] 1,2,4-triazepines,[6] pyridines,[7] various fused heterocycles,[8] nucleosides[9] etc. Commonly, compounds **1** were prepared by the addition of thiocyanic acid generated by treatment of thiocyanate salts with strong mineral acids to α,β-unsaturated aldehydes and ketones in water.[10,11] However, success of this reaction is highly dependent on the substrate structure, particularly on the nature of substituents. For example, the presence of aryl group(s) due to conjugation would cause significant hindrance for the addition of HNCS. Indeed, the synthesis of some isothiocyanates **1** starting from alkyl-substituted unsaturated carbonyl compounds was described in the literature; however, there are only few reports on preparation of aryl substituted isothiocyanates **1**. Benzylidene acetone, *p*-anisylidene acetone, and benzylidene acetophenone (chalcone) failed to give any adducts with HNCS under a wide variety of reaction conditions.[10] In contrast, Sammour et al. described the reaction of chalcone with HNCS afforing 3-isothiocyanato-1,3-diphenylpropan-1-one (**2**) in 54% yield.[12] The structure of this compound was established by elemental analysis and some chemical transformations. Later, Weber et al. prepared isothiocyanate **2** from chalcone under Sammour's conditions and provided selected IR and ^{1}H NMR spectroscopic data for the product.[13] To date there are no reports describing the addition of HNCS to other chalcones.

In continuation of our research in the synthesis of cyclic (thio)semicarbazones[14] we were interested in preparation of 1,3-diaryl-substituted 3-isothiocyanatopropan-1-ones. First, we attempted to obtain isothiocyanate **2** from unsubstituted chalcone under the described conditions (chalcone/H_2SO_4/ NH_4NCS molar ratio = 1:1:3.3, water, rt, 3 h).[12] However, according to ^{1}H NMR spectroscopic data, the crude product contained 95% of the starting material and only 5% of isothiocyanate **2**.

Thus, the reaction of chalcones with HNCS had to be reinvestigated to develop simple and general procedure for the preparation of 1,3-diaryl-3-isothiocyanatopropan-1-ones. Here, we report the results of this reinvestigation.

Results and discussion

Chalcones **3a-i** which were readily prepared by base-catalyzed condensation of the corresponding acetophenones and aromatic aldehydes were used as starting materials.[15] They reacted with aqueous thiocyanic acid generated in situ by treatment of thiocyanate ammonium with dilute sulfuric acid to give the target 1,3-diaryl-3-isothiocyanatopropan-1-ones **4a-i** (Scheme 1). This reaction proceeded under heterogeneous conditions, and its result (yield and purity of **4a-i**) depended on a number of factors, including molar ratio of reagents, concentration, temperature, and reaction time (Table 1). It should be noted that small amounts of byproducts identified as 3,4-dihydro-2*H*-1,3-oxazine-2-thiones **5a-i** formed in this reaction.



Scheme 1. Synthesis of β-isothiocyanato ketones **4a-i** from chalcones **3a-i**.

Table 1. Synthesis of β-isothiocyanato ketones **4a-i** by reaction of chalcones **3a-i** with NH_4NCS and H_2SO_4 in water.

Entry	3	R	R^1	R^2	Conc. of **3** (mol/L)	**3**/NH_4NCS/H_2SO_4 molar ratio	Reaction conditions	Products distribution[a]			Yield of **4** (%)[b]
								4	**5**	**3**	
1[c]	**3a**	H	H	H	1.338	1.00:3.31:1.00	3 h, rt	5	0	95	-
2	**3a**	H	H	H	0.249	1.00:6.15:3.17	1 h, 50 °C	2	0	98	-
3	**3a**	H	H	H	2.636	1.00:6.03:3.07	3 h, 50 °C	79	4	17	59
4	**3a**	H	H	H	2.637	1.00:6.09:3.19	24.33 h, rt	96	2	2	74
5[d]	**3b**	H	Me	H	0.241	1.00:12.08:6.09	3 h, 70 °C	19	2	79	-
6[d]	**3b**	H	Me	H	0.249	1.00:5.99:3.01	6 h, 70 °C	14	0	86	-
7[d]	**3b**	H	Me	H	0.228	1.00:6.00:3.04	3 h, 70 °C	13	0	87	-
8	**3b**	H	Me	H	2.636	1.00:6.02:3.18	3 h, 50 °C	63	4	33	45
9	**3b**	H	Me	H	2.645	1.00:6.08:3.21	1 h, 50 °C	52	2	46	40
10	**3b**	H	Me	H	2.639	1.00:12.03:6.06	3 h, 50 °C	62	12	26	42
11	**3b**	H	Me	H	5.269	1.00:6.06:3.43	3 h, 50 °C	66	8	26	45
12	**3b**	H	Me	H	2.634	1.00:6.09:3.19	1 h, 70 °C	49	3	48	38
13	**3b**	H	Me	H	2.635	1.00:6.14:3.24	3 h, 70 °C	49	4	47	30
14	**3b**	H	Me	H	2.643	1.00:6.09:3.03	3 h, rt	37	0	63	28
15	**3b**	H	Me	H	2.634	1.00:6.17:3.26	24 h, rt	81	3	16	62
16	**3c**	H	OMe	H	2.644	1.00:6.09:3.18	3 h, 50 °C	50	3	47	45
17	**3c**	H	OMe	H	2.639	1.00:6.29[e]:6.06	2 h, 50 °C	69	9	22	42
18	**3c**	H	OMe	H	2.637	1.00:6.09:3.25	24 h, rt	65	3	32	55
19	**3d**	OMe	OMe	H	2.648	1.00:6.54:3.20	3 h, 50 °C	60	4	36	42
20	**3d**	OMe	OMe	H	2.635	1.00:6.13:8.36	3 h, 50 °C	63	13	24	-
21	**3d**	OMe	OMe	H	2.643	1.00:6.17:6.34	1.5 h, 50 °C	66	11	23	44
22	**3e**	H	*t*-Bu	H	2.634	1.00:6.14:3.05	24 h, rt	76	3	21	64
23	**3f**	H	H	Me	2.627	1.00:6.03:3.15	3 h, 50 °C	79	3	18	58
24	**3f**	H	H	Me	2.633	1.00:6.03:3.18	23 h, rt	93	1	6	66
25	**3g**	H	Me	Me	2.641	1.00:6.12:3.17	3 h, 50 °C	68	3	29	44
26	**3g**	H	Me	Me	2.645	1.00:6.18:3.28	24 h, rt	82	4	14	60
27	**3g**	H	Me	Me	2.640	1.00:6.15:3.30	48 h, rt	83	5	12	61
28	**3h**	H	OMe	Me	2.637	1.00:6.15:3.29	2 h, 50-35 °C; 22 h, 35 °C	69	4	27	49
29	**3h**	H	OMe	Me	2.637	1.00:6.13:6.28	22.5 h, rt	76	12	12	41
30	**3h**	H	OMe	Me	2.644	1.00:6.19:3.74	1.5 h, 50 °C	58	2	40	45
31	**3i**	OMe	OMe	Me	2.643	1.00:6.13:6.34	5 min, 50 °C; 22.5 h, rt	72	10	18	45
32	**3i**	OMe	OMe	Me	2.637	1.00:6.15:6.53	3 h, 50 °C	64	11	25	40
33	**3i**	OMe	OMe	Me	2.646	1.00:6.18:6.63	1.5 h, 50 °C	68	10	22	44

[a] According to ^{1}H NMR spectroscopic data for the crude product.
[b] Yield after purification of the crude product using column chromatography.
[c] This experiment was carried out under the described conditions.[12]
[d] A mixture of H_2O/AcOH (1:1, v/v) was used as a solvent.
[e] 3.02 equivalents of NH_4NCS were added at the beginning of the reaction then 1.06, 1.09, and 1.12 equivalents were subsequently added after 30, 40, and 50 min.

Our initial experiments showed that reaction of **3b** with HNCS did not proceed when the reaction mixture was a suspension [H_2O, **3b**/NH_4NCS/H_2SO_4 in a ratio of 1.00:5.11:2.59 or 1.00:5.05:5.07, 24 h, rt; H_2O, **3b**/NH_4NCS/H_2SO_4 in a ratio of 1.00:3.02:1.40 or 1.00:6.16:3.12, 3 h, 70 °C; H_2O/AcOH (1:1, v/v), **3b**/NH_4NCS/H_2SO_4 in a ratio of 1.00:3.08:1.58, 3 h, 70 °C]. Based on the experience in preparation of some other 3-isothiocyanatoketones which proceeded with emulsion of starting ketone in aqueous media, we attempted to obtain the reaction mixture with **3b** as an emulsion. To achieve this we increased the reaction temperature to 70 °C (H_2O, **3b**/NH_4NCS/H_2SO_4 in a ratio of 1.00:3.02:1.40 or 1.00:6.16:3.12, 3 h), but no emulsion formed. We applied AcOH as a co-solvent, and only with more than 6 equivalents of HNCS emulsions were obtained (entries 5, 6, and 7); however, the reaction proceeded in a small extent. The use of two-phase systems (Et_2O/H_2O, **3b**/NH_4NCS/H_2SO_4 in a ratio of 1.00:10.31:5.21, 3 h, rt; $CHCl_3/H_2O$, **3b**/NH_4NCS/H_2SO_4 in a ratio of 1.00:3.15:1.61, 3 h, reflux) gave no products.

With low-melting chalcone **3a** (mp 56–57 °C) emulsion was obtained by heating the reaction mixture at 50 °C without addition of AcOH, but still only trace amount of isothiocyanate **4a** formed (entry 2). A decrease in the volume of water in this reaction led to formation of the desired product in considerable amounts (entry 3). Thus, isothiocyanate **4a** was prepared from chalcone **3a** in 59% isolated yield. It is noteworthily that neutralization of the reaction mixture with aqueous $NaHCO_3$ during the extractive work-up did not cause decomposition of the product. Otherwise, ^1H NMR spectroscopic data always showed the presence of acid in the crude product regardless the number of washings of the extract with H_2O.

Under conditions described for **3a**, chalcones **3b-d,g** gave the corresponding isothiocyanates **4b-d,g** in 42–45% isolated yields (entries 8, 16, 19, and 25). Then, we attempted to optimize the reaction conditions. With chalcone **3b** a twelvefold excess of HNCS (entry 10) or further decrease in the volume of water in the reaction mixture (entry 11) had no effect on the isolated yield of **4b**. An increase in the reaction temperature to 70 °C (entry 8 vs entry 13) caused a decrease in the yield of **4b** from 45 to 30%, while a decrease in the reaction time at 70 °C led to an increase in the yield of **4b** (entry 13 vs entry 12). From comparison of entries 8 and 9 it was clear that further increase in the reaction time at 50 °C would not lead to any increase in the yield of **4b**. We suppose that some kind of equilibrium between chalcone **3b** and isothiocyanate **4b** was reached in the reaction mixture at 50 °C after 3 hours. Since aqueous solutions of HNCS were reported to be unstable at high concentrations,[16] with chalcone **3c** we tried the addition of NH_4NCS to the reaction mixture in portions (entry 17), but this had no effect on the isolated yield of **4c** (entry 17 vs entry 16). At room temperature the addition of HNCS to chalcone **3b** proceeded slower than at heating (entry 14 vs entry 8); however, an increase in the reaction time from 3 to 24 h led to a considerable increase in the isolated yield of isothiocyanate **4b** (entry 14 vs entry 15). With chalcone **3g**, further increase in the reaction time (from 24 h to 48 h) had no effect on the yield of product **4g** (entry 26 vs entry 27).

At room temperature chalcones **3a-c**,**e-g** formed emulsions under conditions applied (entries 4, 15, 18, 22, 24, 26); however, under similar conditions for chalcones **3d**,**h**,**i** the reaction mixtures were suspensions. Therefore, the reaction mixtures were heated at 50 °C. Emulsions formed in all cases but with chalcone **3i** six equivalents of H_2SO_4 were used to obtain emulsion. For chalcone **3d** a decrease in the reaction time and the use of six equivalents of H_2SO_4 led to a slight increase in the yield of **4d** (entry 19 vs entry 21). Though the reaction of **3h** with HNCS could be performed at room temperature, but presumably because of great excess of H_2SO_4 which could cause some side reactions, the isolated yield of isothiocyanate **4h** did not differ significantly from that obtained under heating (entry 29 and entry 30). The same effect of temperature was observed for compound **3i** (entry 31 vs entry 33); heating for 5 minutes at the beginning of the reaction (entry 31) was used to obtain emulsion which retained at room temperature. A decrease in the reaction time under heating (entry 32 vs entry 33) led to a slight increase in the yield of isothiocyanate **4i**.

The differences between the isolated yields and the amount of isothiocyanates in the crude products determined by ^1H NMR spectroscopy (Table 1) can be explained by resinification of organic materials which proceeded in some extent under the action of strong acids during the reactions. Partial destruction of organic materials under acidic conditions could be seen from the comparison of entries 29 and 30 (for **3h**), entries 16, 17, and 18 (for **3c**). In all cases the mixtures transformed from fine light orange emulsions into dense brown oils; with methoxy-derivatives **3c,d,h,i** they became dark brown. All isothiocyanates **4a-i** were isolated using silica gel column chromatography. In all cases isolation was not tedious since the products cleanly left the columns before all other components of the mixture. It should be noted that purification of the crude product using crystallization can be performed only with isothiocyanate **4a** but it does not remove the coloring of product.

The data obtained show that the reaction of chalcones **3a-i** with HNCS was always accompanied by formation of the corresponding dihydro-1,3-oxazine-2-thiones **5a-i** (Table 1) whose structure was assigned on the basis of NMR spectroscopic data. The amount of oxazines increased with an increase in the amount of H_2SO_4 in the reaction mixtures (entry 8 vs entry 10; entry 19 vs entry 21). Further increase in the acidity of reaction media (2 additional equivalents of H_2SO_4 over NH_4NCS, entry 20) had only a slight effect on the amount of oxazine (entry 20 vs entry 21). Prolongation of the reaction had a negligible effect on the amount of oxazines (entry 32 vs entry 33; entry 14 vs entry 15). Under all test conditions the amount of oxazines **5a-i** did not exceed 13 mol% (^1H NMR spectroscopic data). We suppose that these compounds formed via the enol forms of isothiocyanato ketones **4a-i** followed by their intramolecular cyclization.

Conclusion

Practical synthesis of 1,3-diaryl-substituted 3-isothiocyanatopropan-1-ones based on the reaction of chalcones with thiocyanic acid generated in situ by treatment of thiocyanate ammonium with dilute sulfuric acid has been developed. Principal condition for successful proceeding of the reaction is the formation of emulsion in the reaction mixture. It should be stressed that its formation does not depend on the melting point of the starting chalcone as evidenced by our data. The optimal overall volume of H_2O was found to be 0.38 mL per 1 mmol of chalcone, and the chalcone/NH_4NCS/H_2SO_4 molar ratio was found to be 1:6:3. If emulsion did not form at room temperature under these conditions, first, slight heating at 50 °C for 1.5 h should be applied, second, 3 equivalents of H_2SO_4 should be added.

We hope that this research will be helpful in the preparation of a large variety of 1,3-diaryl-3-isothiocyanatopropan-1-ones from readily available chalcones. These isothiocyanato ketones could serve as a versatile starting material in organic synthesis.

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