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Sulfur promoted decarboxylative thioamidation of carboxylic acids using formamides as amine proxy

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ABSTRACT

An efficient decarboxylative thioamidation of arylacetic and cinnamic acids has been developed employing formamides as amine surrogate and sulfur as promoter. Thioamides with variant structural features are obtained under mild reaction conditions without the use of transition metal catalysts and oxidants.

1. Introduction

The advancement of new and efficient reactions without compromising the product selectivity and environmental safety is the recent trend in synthetic research. Cross-coupling and C–H activation reactions have turned out to serve the purpose primarily.[1] Thioamide moiety is ubiquitous in biologically active molecules, and is widely used as synthetic building block for many heterocycles, besides its industrial applications.[2] Different methods for the preparation of thioamides are described in literature, the most common being the Willgerodt–Kindler reaction,[3] thionation reaction,[4] and the reaction of CS_2 with Grignard reagents.[5] Since these methods often require harsh conditions, some useful thioamide forming reactions have been recently reported employing aldehyde,[6] benzylamine,[7] and alkyne/alkene[8] as starting material. Yet, the development of greener and practical methods to prepare thioamides from new and readily available starting materials is desirable and demanding.

Decarboxylative coupling reactions have attracted a great deal of attention and offer potential advantages since (i) carboxylic acids are inexpensive and readily available with great structural diversity both from natural and synthetic sources, (ii) they are easy to handle and store (iii) CO_2 is the only by product, which is non–flammable and is easily removed from the reaction mixture.[9]

However, most of the decarboxylation reactions developed so far necessitate the use of transition metals as catalysts.[10] Recently, our group has developed the synthesis of thioamides using arylacetic/cinnamic acids and amines as coupling partners in the presence of simple sulfur.[11b] However, a practical problem arises in case of dimethylamine, which exists either in gaseous form or is commercially available as aqueous solution. Therefore, a viable substitute is looked for. Since the development of efficient reactions utilizing readily available starting materials is always imperative, the use of DMF as amine source has recently been described.[12] In view of the above, and as a part of our ongoing endeavor to develop novel strategies,[13] particularly the synthesis of thioamides,[11b,14] we disclose herein a practical synthesis of thioamides using formamides as amine source adopting a decarboxylation protocol in the presence of elemental sulfur and K_2CO_3 (Scheme 1).

2. Results and discussion

To begin with, a model reaction employing phenylacetic acid (**1a**) and dimethylformamide (**2a**) was carried out in the presence of elemental sulfur (S_8, Mol. wt 32) and K_2CO_3 under solvent-free conditions at 120 °C. To our delight, the desired product **3a** was obtained in 76% yield (Table 1, entry 1). The reaction conditions were then thoroughly optimized by varying different parameters such as promoter, solvent, and base; and the overall findings are summarized in Table 1.

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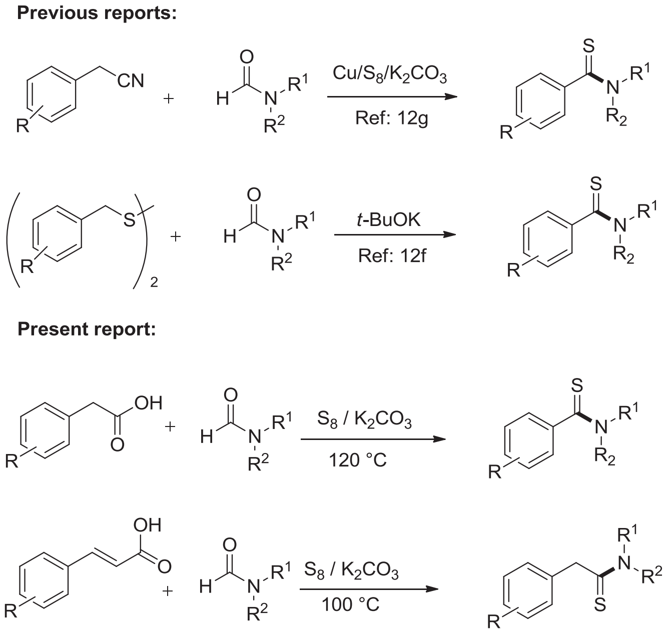
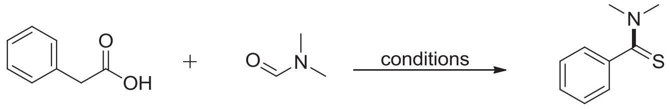


Scheme 1. Thioamidation using formamides.

Absence of base or altering K_2CO_3 to Na_2CO_3 or DABCO did not bring about any positive change (entries 2, 3 & 4). Making use of different solvents was also worthless, as it rather reduced the yields considerably (entries 5 to 10), although the use of 1,4-dioxane and pyridine had little diminution effect as compared to DMSO, toluene, acetic acid, and *t*-BuOH. Addition of some copper metal salts to sulfur also reduced the product yields significantly (entries 11, 12 & 13). After having established the optimized conditions (Table 1, entry 1), the generality of the reaction was examined using diversely substituted arylacetic acids (**1**) and formamides (**2**) to provide the corresponding thioamides **3** in 52–81% yield (Table 2). Arylacetic acids containing both the electron-rich and electron-deficient substituents on aromatic ring (**1a**–**k**) underwent the reaction smoothly to afford the thioamidated products **3a**–**n**. However, the reaction of **1e** under standard conditions did not succeed and required a change in base from K_2CO_3 to DABCO to afford the desired product **3e**. The substituent such as 4-OH (**1g**), 4-F (**1h**) and 4-Ph (**1j**) were well tolerated during the course of reaction, but the NO_2 group (**1d** & **1k**) was eventually reduced to NH_2 (**3d** & **3k**). A heteroaromatic acid viz., thiophene-3-acetic acid (**1i**) also participated nicely in the reaction. However, indole-3-acetic acid, α-naphthyl acetic acid and valeric acid did not give rise to the desired product. Formamides such as *N*-formyl morpholine (**2c**) and *N*-formyl piperidine (**2b**) also reacted well to provide the corresponding tertiary thioamides (**3m** & **3n**) in reasonably high yields.

Table 1
Optimization of the reaction conditions[a]



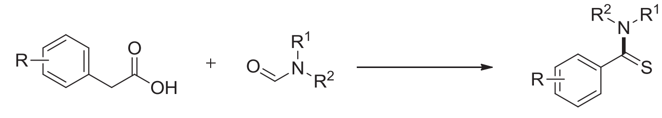
1a **2a** **3a**

Entry	Promoter	Solvent	Base	Yield (%)[b]
1	S_8	—	K_2CO_3	76
2	S_8	—	—	31
3	S_8	—	Na_2CO_3	53
4	S_8	—	DABCO	68
5	S_8	DMSO	K_2CO_3	16
6	S_8	Toluene	K_2CO_3	20
7	S_8	1,4-Dioxane	K_2CO_3	62
8	S_8	Pyridine	K_2CO_3	72
9	S_8	Acetic acid	—	0
10	S_8	*t*-BuOH	K_2CO_3	25[c]
11	CuI+S_8	—		23
12	CuBr+S_8	—		30
13	$Cu(OAc)_2\cdot 2H_2O$+S_8	—		26

[a] Reaction conditions: **1** (1 mmol), **2** (1 mL), base (2 equiv), S_8 (4 equiv), Solvent (1 mL), Cu (10 mol %), 120 °C, 24 h.
[b] Isolated yield after column chromatography.
[c] 100 °C.

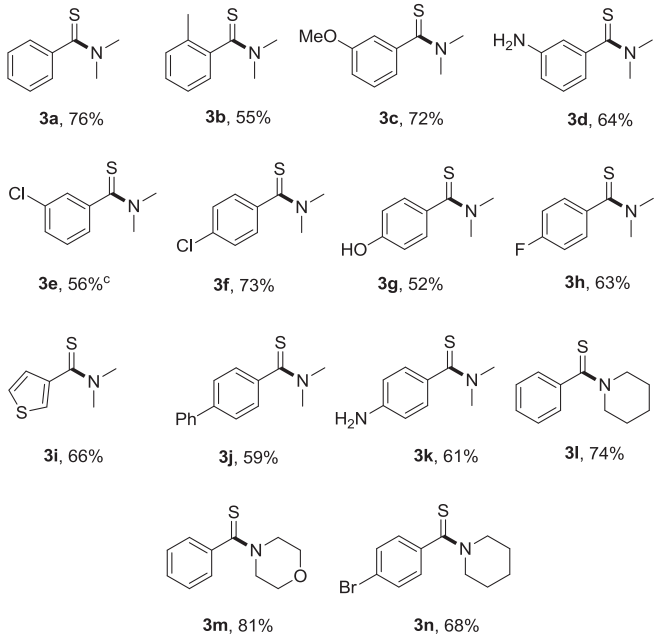
To extend the scope of the reaction, the optimized conditions were then applied to the reaction of cinnamic acid derivatives (**4a**–**4g**) with formamides **2a**. Gratifyingly, cinnamic acids bearing different electronic and steric properties (**4a**–**4g**) underwent the reaction smoothly to afford the corresponding thioamides (**5a**–**5f**) in reasonably good yields (Table 3). The NO_2 group in the substrate **4e** was again reduced to NH_2 (**5e**). Surprisingly, the compound **4g**

Table 2
Scope of the reaction with arylacetic acids[a]



1 **2** **3**

R = H (**1a**), R = 2-Me (**1b**), R = 3-OMe (**1c**)
R = 3-NO_2 (**1d**), R = 3-Cl (**1e**), R = 4-Cl (**1f**)
R = 4-OH (**1g**), R = 4-F (**1h**), 3-thiophenyl (**1i**)
R = 4-Ph (**1j**), R = 4-NO_2 (**1k**), R = 4-Br (**1l**)
$R^1 = R^2$ = Me (**2a**), *N*-formylpiperidine (**2b**)
N-formylmorpholine (**2c**)



3a, 76% **3b**, 55% **3c**, 72% **3d**, 64%
3e, 56%[c] **3f**, 73% **3g**, 52% **3h**, 63%
3i, 66% **3j**, 59% **3k**, 61% **3l**, 74%
3m, 81% **3n**, 68%

[a] Reaction conditions: **1** (1 mmol), **2** (1 mL), K_2CO_3 (2 equiv), S_8 (4 equiv), 120 °C, 24 h.
[b] Isolated yield after column chromatography.
[c] DABCO was used.