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Functionalization of activated methylene C–H bonds with nitroarenes and sulfur for the synthesis of thioamides†

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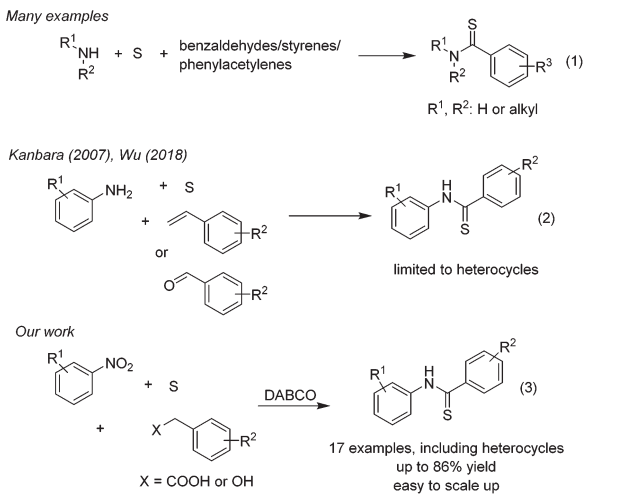
We report a method to obtain arylthioamides by the functionalization of sp^3 C–H bonds in phenylacetic acids and benzyl alcohols. Reactions proceeded without the use of any solvents and were compatible with many functionalities and heterocycles. These conditions allow for a rapid synthesis of thioamides from simple, commercial substrates.

Thioamides are prevalent structures found in biologically active compounds, pharmaceutical molecules, agricultural chemicals, and sensor systems.[1] Yet, their functionalities could be used as valuable intermediates for the synthesis of heterocycles or complex structures.[2] Thionation of C=O bonds in amides using Lawesson's reagent or isosteric phosphorus–sulfur complexes is perhaps the most common method to obtain thioamides.[3] Benzothioamides could be obtained from the Friedel–Crafts substitution of arenes with isothiocyanates or the Willgerodt–Kindler reaction.[4] However, the transformations suffer from the limitation of substrate scope, as aliphatic amines or amides are commonly used (eqn (1), Scheme 1). Only a few studies have described the preparation of *N*-arylthioamides from readily available reagents.[5] Singh and co-workers reported one example of *N*-arylthioamides obtained from sulfur-mediated thioamidation of 2-aminopyridine.[5a] Sodium sulfide-catalyzed condensation of anilines and aromatic aldehydes in the presence of elemental sulfur has been reported.[5b] Chen and Wu have presented a rare method for the coupling of anilines, styrenes, and elemental sulfur, affording thiobenzanilides (eqn (2), Scheme 1).[5c] Notably, the conditions used in the last two examples were not compatible with electron-poor or heterocyclic substrates.

Until now, the known methods for the synthesis of *N*-arylthioamides commonly start with anilines. It has been shown that primary aromatic amines are prone to oxidation.[6] Yet, anilines often require prior hydrogenation of nitroarenes. It will be beneficial if nitroarenes could be used for the synthesis of thioamides, thus shortening the synthetic schemes. Examples showing the uses of nitroarenes in C–N bond formation have been recently disclosed. In 2015, a pioneering study by Baran described an iron-catalyzed hydroamination of olefins with nitrobenzenes, nitropyrroles, and nitroindoles.[7a] Nickel-promoted relay amination has also been reported.[7b] Later, Driver,[7c] Niggemann,[7d] Radosevich,[7e] and Hu[7f] reported the methods for reductive coupling of aryl/alkyl halides or arylboronic acids with nitroarenes to afford arylamines. Despite these successes, the transformations are still limited due to the need for strong, hygroscopic reductants such as zinc or hydrosilanes.

Metal-free, sulfur-mediated synthesis of benzothiazoles and sultams using *ortho*-halo or *ortho*-alkenyl nitroarenes has been



Scheme 1 Elemental sulfur-mediated synthesis of thioamides.

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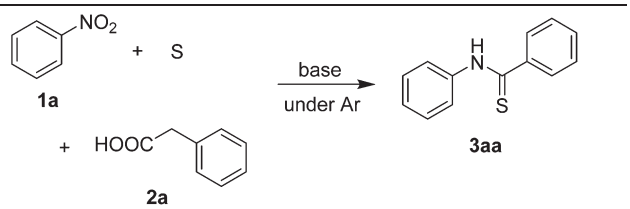
reported.[8] The reactions presumably proceeded through a nucleophilic substitution of a sulfide anion, followed by a nitro reduction and an electrophile trapping. We speculated that if a thiobenzaldehyde is formed, quenching of the intermediate with a nucleophilic nitrogen source would afford *N*-arylthioamide. Formation of thiobenzaldehyde intermediates was possible when phenylacetic acids were condensed with elemental sulfur in the presence of a tertiary amine.[8d] We report here a method for the synthesis of thioamides from simple nitroarenes, elemental sulfur, and arylacetic acids or benzyl alcohols (eqn (3), Scheme 1). Reactions occurred in the presence of the DABCO base. The combination of abundant and stable nitroarenes with environmentally benign and non-toxic elemental sulfur without additional organic solvents is the important advantage of the protocol.

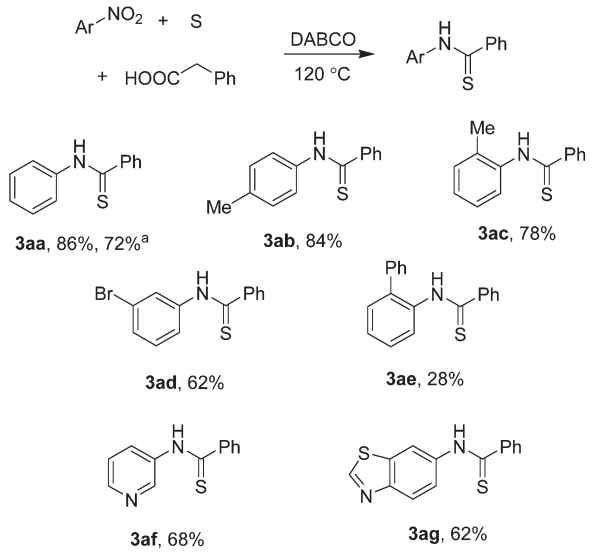
We commenced our investigation by exploring the synthesis of *N*-phenylbenzothioamide (**3aa**) from the coupling of nitrobenzene (**1a**), phenylacetic acid (**2a**), and elemental sulfur. The reaction optimization was carried out with respect to the base, amount of the base, amount of sulfur, and reaction temperature (Table 1). Sodium acetate (entry 1) and potassium carbonate (entry 2) were inferior bases to aliphatic amines and N-heterocycles. Complexation with amines presumably increases the nucleophilicity of elemental sulfur.[8] Among an array of amine bases (entries 3–8), DABCO gave the best yield of **3aa**. Lowering the amount of DABCO decreased the product yield (entries 9 and 10). Using less than 2 equivalents of sulfur afforded sluggish mixtures (entries 11 and 12). Lastly, running the reaction at temperatures lower or higher than 120 °C plummeted the yield of **3aa** (entries 13–15).

Table 1 Studies of the reaction conditions[a]



Entry	Base	Sulfur amount, (equiv.)	Temperature (°C)	Yield of **3aa** (%)
1	NaOAc	2	120	Trace
2	K_2CO_3	2	120	12
3	1-Methylimidazole	2	120	24
4	*N*-Methylpiperidine	2	120	50
5	*N*,*N*′-Dimethylpiperazine	2	120	52
6	$EtiPr_2N$	2	120	16
7	DBU	2	120	36
8	DABCO	2	120	94
9[b]	DABCO	2	120	89
10[c]	DABCO	2	120	59
11	DABCO	1.5	120	89
12	DABCO	1	120	60
13	DABCO	2	100	70
14	DABCO	2	80	23
15	DABCO	2	140	41

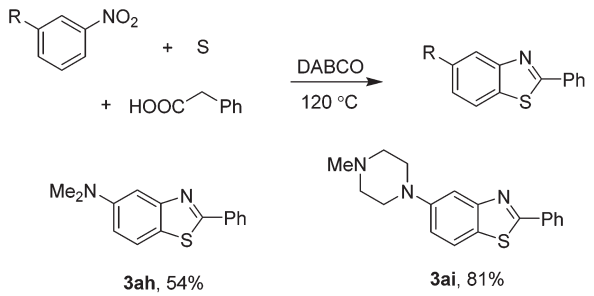
[a] Nitrobenzene (0.5 mmol), base (1 mmol), under argon for 16 h. Yields are GC yields using a diphenyl ether internal standard. [b] DABCO (0.75 mmol). [c] DABCO (0.5 mmol).



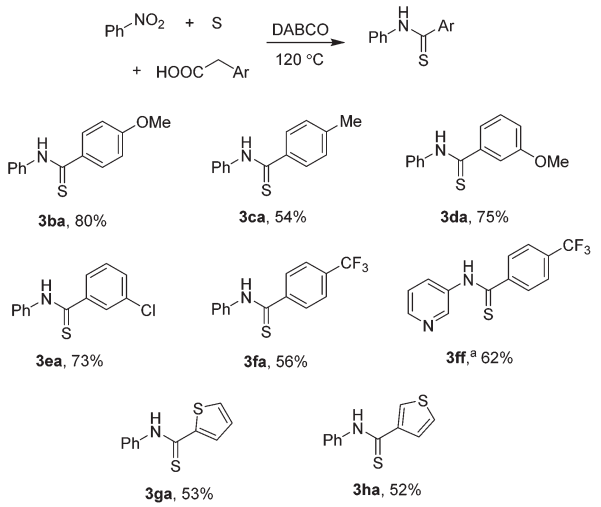
Scheme 2 Reaction scope with respect to nitroarenes. Reagents and conditions: Nitroarenes (0.5 mmol), phenylacetic acid (0.75 mmol), sulfur (1 mmol, 32 g mol^{-1}), DABCO (0.5 mmol), under Ar, 120 °C, 16 h. Yields are isolated yields. Please see the ESI for more details. [a] 1.5 mmol scale.

The scope of nitroarenes is studied next and presented in Scheme 2. Either electron-rich (**3ab** and **3ac**) or electron-poor (**3ad**) substrates afforded thioamides in good yields. A low yield of thioamide **3ae** was obtained when phenylacetic acid was coupled with a sterically hindered 2-nitrobiphenyl. The transformation could offer a rare method for the rapid synthesis of thioamide-containing heterocycles. Products derived from 3-nitropyridine (**3af**) and 6-nitrobenzothiazole (**3ag**) were obtained in moderate yields. If 3-nitro-*N*,*N*′-dialkylanilines were used, the major products were 2-phenylbenzothiazole derivatives (**3ah** and **3ai**, Scheme 3), possibly obtained through electrophilic cyclization of electron-rich thioamide.[9]

Studies on phenylacetic acids were also performed. The scope of the substrates is illustrated in Scheme 4. Successful thioamidation of arylacetic acids was achieved regardless of



Scheme 3 Synthesis of 2-phenylbenzothiazoles.

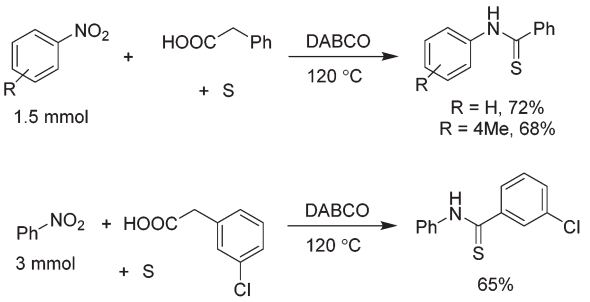


Scheme 4 Reaction scope with respect to arylacetic acids. Reagents and conditions: Nitrobenzene (0.5 mmol), arylacetic acid (0.75 mmol), sulfur (1 mmol, 32 g mol^{-1}), DABCO (0.5 mmol), under Ar, 120 °C, 16 h. Yields are isolated yields. Please see the ESI for more details. [a] 3-Nitropyridine (0.5 mmol).

the electronic properties of aryl moieties. Most of the *para*- and *meta*-substituted phenylacetic acids were competent substrates, while *ortho*-methyl phenylacetic acid failed to give the product. Functionalities such as methoxy (**3ba** and **3da**), methyl (**3ca**), chloro (**3ea**), and trifluoromethoxy (**3fa** and **3ff**) were tolerant to the reaction conditions. Thiophenylacetic acids successfully coupled with nitrobenzene to afford thioamides (**3ga** and **3ha**), showing the compatibility of heteroaryl acetic acids. Scaling up of the reactions was also attempted and is presented in Scheme 5. Products were isolated without a dramatic decrease in the yields.

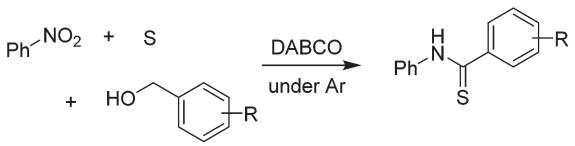
Functionalization of methylene sp^3 C–H bonds in benzyl alcohols was also viable and is presented in Table 2. These reactions required excess amounts of nitroarenes and afforded arylthioamides in moderate yields (entries 1–4). Notably, the use of heterocyclic nitroarenes failed to give the product (entry 5). Studies on the reaction conditions to expand the scope of benzyl alcohols are ongoing.

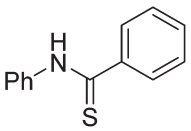
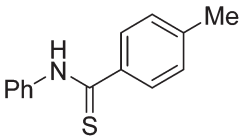
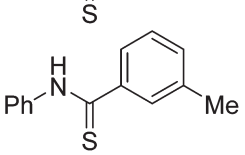
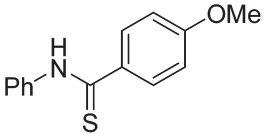
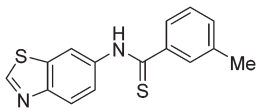
Shibahara and Murai reported that thionation of carboxamides with elemental sulfur was possible should a strong



Scheme 5 Large-scale synthesis of thioamides.

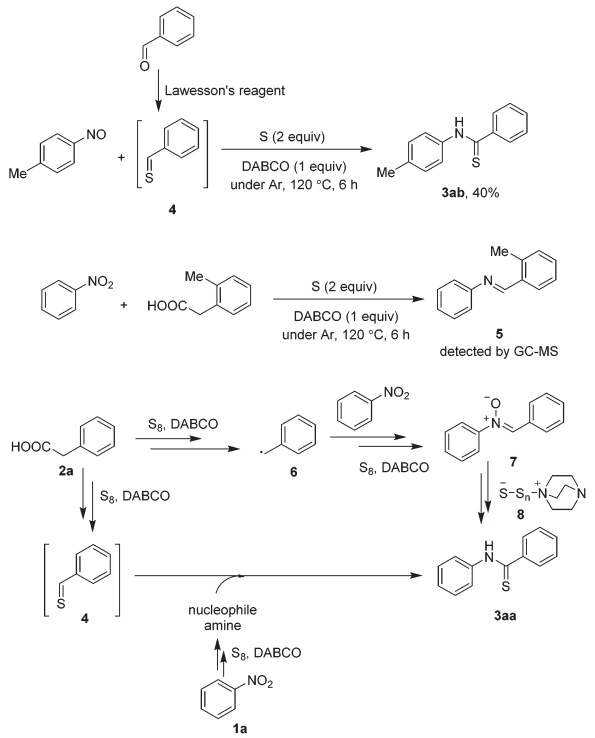
Table 2 Synthesis of arythioamides from benzyl alcohols[a]



Entry	R	Product	Compound, yield (%)
1	H		**3aa**, 60
2	4Me		**3ca**, 42
3	3Me		**3ia**, 47
4	4MeO		**3ba**, 52
5[b]	3Me		**3ig**, trace

[a] Benzyl alcohols (0.5 mmol), nitrobenzene (1 mmol), sulfur (1.5 mmol, 32 g mol^{-1}), DABCO (1 mmol), under Ar, 120 °C, 16 h. Yields are isolated yields. [b] 6-Nitrobenzothiazole (1 mmol).

reductant such as hydrochlorosilanes be used.[10a] Such a sulfur transfer did not occur under our conditions, since no trace of carboxamides was found with or without sulfur. Thus, our initial thought on the reaction mechanism (Scheme 6) was that thioaldehyde was possibly formed by the reaction of phenylacetic acid and elemental sulfur,[8d] followed by amine-type nucleophilic addition (**2aa** → **4** → **3aa**). Alternatively, nitrobenzene coupled with phenylacetic acid to give the nitroalkane radical intermediate (**2aa** → **6** → **7**) which was then trapped by the DABCO–sulfur complex **8**.[10b] Some control experiments were carried out to differentiate the possibilities. Trapping benzothialdehyde with nitrosobenzene furnished thioamide in 40% yield.[11] It should be noted that, unlike the example shown by McLaughlin,[12] aniline was not obtained from a simple reduction of nitrobenzene.[13] Meanwhile, *N*-phenyl-1-(*o*-tolyl)methanimine **5**, detected by GC-MS, was the major product from the reaction using an *ortho*-methyl phenylacetic acid substrate. Nguyen and co-workers described that *ortho*-substituted phenylacetic acids failed to react with elemental sulfur,[8d] presumably because the nucleophilic addition of the amine–sulfur adduct to hindered electrophiles was hampered. We also attempted some experiments to detect the possible radical intermediates.[13] Reactions in the presence of radical



Scheme 6 Mechanistic considerations.

quenchers such as TEMPO or diphenylethylene afforded thioamide in lower yields. More importantly, a product derived from the addition of the benzyl thiol radical to diphenylethylene was observed, somewhat confirming the relevance of the benzyl radical **6** in the reaction. At this moment, the transformation likely proceeded through a nitroalkane radical intermediate, although a mechanism that involves benzothialdehyde followed by the quenching of nitrogen-based nucleophiles cannot be excluded.

Conclusions

In conclusion, we have developed a method for the three-component coupling of nitroarenes, elemental sulfur, and methylene C–H bonds in phenylacetic acids or benzyl alcohols. The reactions proceed in the presence of the DABCO base and are tolerant to many functional groups such as halogens, alkoxy, amine, trifluoromethyl and heterocycles. The use of simple, cheap elemental sulfur in combination with stable, commercial nitroarenes is the prominent benefit of our method compared to the available examples. Studies on the expansion of the reaction scope and on the reaction mechanism will be published later.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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