RSC Advances

PAPER

Cite this: *RSC Adv.*, 2020, **10**, 44743

Synthesis of primary *N*-arylthioglyoxamides from anilines, elemental sulfur and primary C–H bonds in acetophenones†

Khoa M. Tran,[ab] Nguyen H. K. Nguyen,[ab] Thuy T. Bui,[ab] Tuong A. To,[ab] Nam T. S. Phan,[ab] Ha V. Le*[ab] and Tung T. Nguyen*[ab]

Received 14th October 2020
Accepted 7th December 2020

DOI: 10.1039/d0ra08740h

rsc.li/rsc-advances

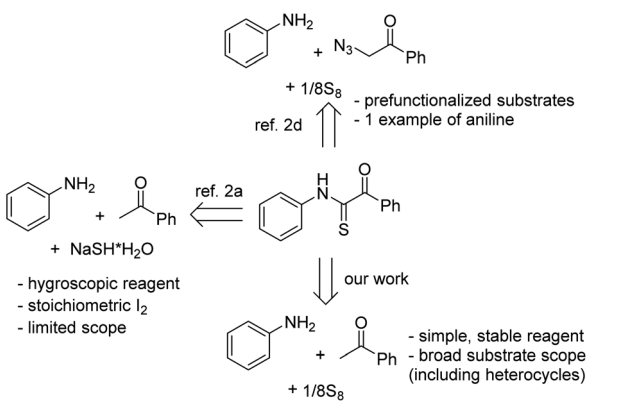
A simple method for coupling of anilines, acetophenones, and elemental sulfur to afford *N*-arylthioglyoxamides has been developed. Reactions proceeded in the presence of Na_2SO_3 and DMSO, thus eliminating the need for transition metals and external oxidants. Functionalities such as halogen, ester, methylthio, and heterocycle groups were compatible with the conditions. Electron-poor acetophenones sometimes gave isosteric glyoxamides.

Primary *N*-arylthioglyoxamides are prominent precursors to afford useful heterocycles.[1] Yet, only a few methods for the synthesis of thioglyoxamides have been reported (Scheme 1).[2] Wu and co-workers described an I_2-mediated coupling of acetophenones, anilines, and sodium hydrosulfide in DMSO to furnish such α-ketothioamides.[2a] The work suffered from the use of a hygroscopic reagent as well as the formation of a toxic by-product, dimethyl sulfide. An aerobic, iron-catalyzed sulfuration/amination of sp^3 C–H bonds in acetophenones with elemental sulfur, a somewhat friendlier agent than sodium hydrosulfide, was later disclosed.[2b] Notably, the scope of amines was limited to aliphatic compounds. Prefunctionalized, acetophenone-derived molecules such as α-azidoacetophenones or enaminones could be used to couple with elemental sulfur as well.[2c,d] It should be profitable if a method for coupling of simple, commercial substrates and allowing general scopes of substrates is developed, thus *N*-arylthioglyoxamides could be obtained feasibly.

Elemental sulfur mediated functionalization of C–H bonds has been extensively studied. Many examples focus on the synthesis of heterocycles.[3] Methods for using elemental sulfur to obtain S-containing functionalities are recently presented. Nguyen and co-workers reported a couple examples in which oxidative coupling of benzylic C–H bonds in benzyl amines or those in terminal alkynes with elemental sulfur occurred.[4] Such the desired thioamides were affordable *via* redox-neutral processes involving nitroarenes and activated sp^3 C–H bonds in arylacetic acids or picolines.[5] Sulfuration of acidic sp^2 C–H bonds with elemental sulfur is known.[6]

Recently, multicomponent reactions that included elemental sulfur for synthesis of S-heterocycles and other synthetically useful functionalities have been presented.[7] Herein, we report a method for synthesis of *N*-arylthioglyoxamides from commercial anilines, acetophenones, and elemental sulfur. No oxidants or transition metals were required. Such thioglyoxamides could be obtained from nitroarenes as amine surrogates, albeit in low yields.

The study was started with the oxidative coupling of aniline **1a**, acetophenone **2a**, and elemental sulfur. Some results of optimization are presented in Table 1. It should be noted that the desired product was only observed if reactions were run under argon atmosphere. An early attempt to use Na_2CO_3 base afforded the desired product in 13% yield (entry 1). Switching the base to $NaHCO_3$ increased the yield to 28% (entry 2). Organic, tertiary amine bases such as DABCO (entry 3) and *N*,*N*-



Scheme 1 Synthesis of *N*-arylthioglyoxamides.

[a]*Faculty of Chemical Engineering, Ho Chi Minh City University of Technology (HCMUT), 268 Ly Thuong Kiet, District 10, Ho Chi Minh City, Vietnam. E-mail: lvha@hcmut.edu.vn; tungtn@hcmut.edu.vn*

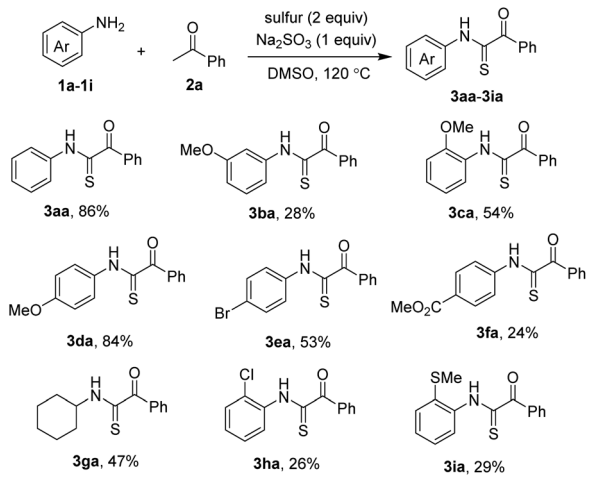
[b]*Vietnam National University Ho Chi Minh City, Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam*

† Electronic supplementary information (ESI) available: Details of experimental procedures, characterization of the products. See DOI: 10.1039/d0ra08740h

Table 1 Studies of reaction conditions[a]

Entry	Base	DMSO amount, (mL)	1a : 2a ratio	Yield of 3aa (%)
1	Na_2CO_3	1	1 : 1.5	13
2	$NaHCO_3$	1	1 : 1.5	28
3	DABCO	1	1 : 1.5	44
4	DiMePi	1	1 : 1.5	34
5	Na_2SO_3	1	1 : 1.5	60
6	NaOAc	1	1 : 1.5	39
7	Cs_2CO_3	1	1 : 1.5	Trace
8[b]	Na_2SO_3	1	1 : 1.5	47
9	Na_2SO_3	1.5	1 : 1.5	61
10	Na_2SO_3	2	1 : 1.5	68
11	Na_2SO_3	3	1 : 1.5	40
12	Na_2SO_3	2	1 : 2	72
13	Na_2SO_3	2	1 : 3	74
14[c]	Na_2SO_3	2	1 : 3	78
15[d]	Na_2SO_3	2	1 : 3	82

[a] **1a** (0.5 mmol), **2a** (0.75 mmol), elemental sulfur (1 mmol, 32 g mol^{-1}), base (1 mmol), DMSO, under argon at 120 °C for 16 h. Yields of **3aa** are GC yields using diphenyl ether internal standard. Abbreviations: DiMePi = *N*,*N*-dimethylpiperazine. [b] 100 °C. [c] 14 h. [d] 8 h.



Scheme 2 Scope of anilines. Conditions: **1a–1i** (0.5 mmol), **2a** (1.5 mmol), elemental sulfur (1 mmol, 32 g mol^{-1}), Na_2SO_3 (1 mmol), DMSO (2 mL), under argon at 120 °C for 14 h. Yields are isolated yields.

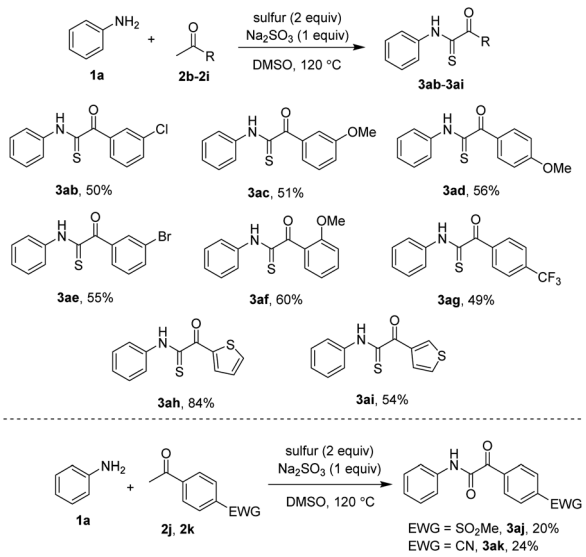
dimethylpiperazine (entry 4) could be used for the sulfurative coupling, albeit furnishing **3aa** in moderate yields. In this reaction, Na_2SO_3 was a superior base, affording the thioglyoxamide in 60% yield (entry 5). Attempts to vary the use of base including NaOAc and Cs_2CO_3 were unsuccessful (entries 6 and 7). Lowering the reaction temperature negatively affected the reaction (entry 8). A prominent effect of DMSO amount was observed (entries 9–11). The reaction should be run with 2 mL of DMSO to obtain a reasonable yield of **3aa**. No other common solvents such as DMF, 1,4-dioxane, or acetonitrile were able to afford the product. Furthermore, increasing the amount of acetophenone was crucial (entries 12 and 13). If 3 equivalents of **2a** was used, the thioglyoxamide **3aa** was obtained in 74% yield (entry 13). The reaction progress was carefully monitored by GC (entries 14 and 15). Notably, it could be stopped at 14 h, since no significant improvement of yield was observed after that.

Scope of the reaction with respect to anilines was next studied. The results are shown in Scheme 2. The unsubstituted *N*-phenylthioglyoxamide **3aa** was isolated in good yield. Methoxy-substituted anilines successfully coupled with acetophenone **1a**; however, yields of the products were varied. Notably, 3-methoxyaniline was much less active than the other two isomers. Bromo-substituted aniline was a competent substrate, giving the product **3ea** that was useful for further modification. Ester functionality was somewhat prone to condition, although isolation of the thioglyoxamide **3fa** was still affordable. Aliphatic amines such as cyclohexylamine could be used, affording the desired sulfurative coupling product **3ga** in 47% yield. *Ortho*- chloro and methylthio anilines were compatible with reaction conditions, albeit giving the thioglyoxamides in low yields (**3ha**, **3ia**).

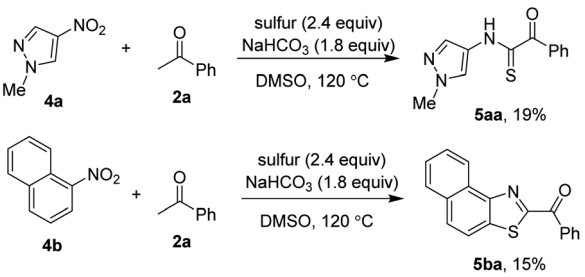
Uses of acetophenones were also investigated (Scheme 3). *Meta*-substituted substrates coupled with aniline **1a** to afford the products in moderate yields (**3ab**, **3ac**, **3ae**). Sterically hindered acetophenones such as **2f** were still compatible with reaction conditions. 4-Methoxy and 4-trifluoromethyl acetophenones successfully furnished the thioglyoxamides, albeit in moderate yields (**3ad**, **3ag**). Heterocycle-derived acetophenones were competent substrates, affording the reasonable yields of the desired products (**3ah**, **3ai**). The conditions were limited to very electron-poor ketones. In those cases, such as that containing SO_2Me (**2j**) and CN (**2k**) groups at the *para* positions to ketones, glyoxamides were the major products (**3aj**, **3ak**).

Our group has shown that nitroarenes could be used as the aniline surrogates in sulfur-mediated functionalization of C–H bonds.[5] Thus, attempts to couple nitro compounds with acetophenones were investigated. However, low yields of products and limited scope of substrates were obtained. Use a nitro-derived imidazole **4a** afforded the thioglyoxamide **5aa** in 19% yield. Notably, the 3-aminopyrazole failed to couple with acetophenone. If a hindered 1-nitronaphthalene **4b** was reacted with acetophenone, a 2-benzoylbenzothiazole derivative **5ab** was isolated. Attempts to develop more efficient conditions for sulfurative coupling of nitroarenes are ongoing.

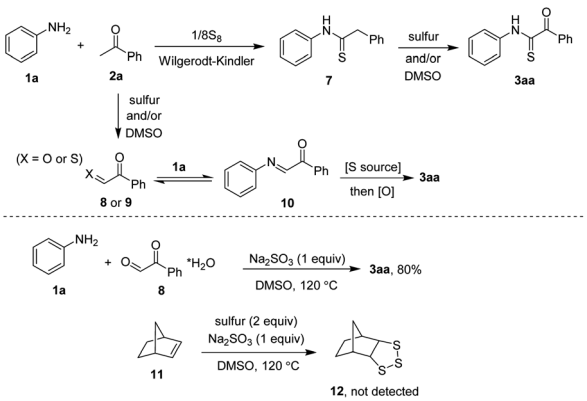
At this moment, two possible pathways were hypothesized as those shown in Scheme 5. Firstly, reaction could occur *via* a conventional Willgerodt–Kindler coupling of **1a** and **2a** to afford the thioamide **7**.[8] This step was in agreement with the result of substrate scope with respect to acetophenones, since electron-poor carbonyl compounds were known to slowly join in the first step.[8b] Oxidation of **7** in the presence of sulfur and/or co-oxidant DMSO would render the desired thioglyoxamide **3aa**. Notably, such the similar pathway was proposed by Nguyen and co-workers.[2b,9] An alternative route could begin with the oxidation of sp^3 C–H bond in **2a** afforded phenylglyoxal **8** or its



Scheme 3 Scope of acetophenones. Conditions: **1a** (0.5 mmol), **2b–2k** (1.5 mmol), elemental sulfur (1 mmol, 32 g mol^{-1}), Na_2SO_3 (1 mmol), DMSO (2 mL), under argon at 120 °C for 14 h. Yields are isolated yields.



Scheme 4 Coupling of nitroarenes and acetophenone. Conditions: **4a** or **4b** (0.5 mmol), **2a** (0.9 mmol), elemental sulfur (1.2 mmol, 32 g mol^{-1}), $NaHCO_3$ (0.9 mmol), DMSO (1.2 mL), under argon at 120 °C for 14 h. Yields are isolated yields.



Scheme 5 Mechanistic consideration.

thio-derived isostere **9**. Imine condensation of this intermediate and **1a** would furnish **10** followed by a sulfur attack and oxidation to afford **3aa**.[10] To clarify this pathway, a control condensation of **1a** and **8** (as a hydrate) was set up. Since desired product **3aa** was obtained in 80% (GC) yield, the oxidation step (**2a** → **8**) could occur during the reaction course. Furthermore, reaction of norbonene **11** with possible trisulfide radical intermediate (**10** → **11**) was unsuccessful.[5b] This result implied that the formation of such a strong nucleophilic sulfide could be excluded.

Conclusions

In conclusion, we have developed a general method to couple anilines, acetophenones, and elemental sulfur to afford *N*-arylthioglyoxamides. The transformation did not need uses of any external oxidants, prefunctionalized substrates, or transition metals. Nitroarenes were also attempted to couple with acetophenones. Control experiments implied the oxidation of α C–H bonds followed by imine condensation or Willgerodt–Kindler-typed sulfuration.

Experimental section

General procedure A (for Schemes 2 and 3)

In a typical experiment, an aniline (0.5 mmol), an acetophenone (1.5 mmol), Na_2SO_3 (126 mg, 1 mmol), elemental sulfur (32 mg, 1 mmol, 32 g mol^{-1}), and DMSO (2 mL) were added to an 8 mL vial equipped with a magnetic stir bar. The vial was flushed with argon for 5 min, capped then placed into a preheated bath (120 °C) and stirred for 14 h. The crude mixture was diluted with ethyl acetate (5 mL) and brine (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was adsorbed onto silica gel (the weight was 10 or 15 times larger than that of the residue) then diluted with hexanes/ethyl acetate to afford the product.

General procedure B (for Scheme 4)

In a typical experiment, a nitroarene (0.5 mmol), acetophenone **2a** (108 mg, 0.9 mmol), $NaHCO_3$ (75 mg, 0.9 mmol), elemental sulfur (38 mg, 1.2 mmol, 32 g mol^{-1}), and DMSO (1.2 mL) were added to an 8 mL vial equipped with a magnetic stir bar. The vial was flushed with argon for 5 min, capped then placed into a preheated bath (120 °C) and stirred for 14 h. The crude mixture was diluted with ethyl acetate (5 mL) and brine (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was adsorbed onto silica gel (the weight was 10 or 15 times larger than that of the residue) then diluted with hexanes/ethyl acetate to afford the product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The Viet Nam National Foundation for Science and Technology Development (NAFOSTED) is acknowledged for supporting this research under project code 104.01-2019.354 (for Ha V. Le).

Notes and references

1 (*a*) X. Feng, Q. Wang, Z.-B. Huang and D.-Q. Shi, *RSC Adv.*, 2014, **4**, 54719; (*b*) M. Li, G.-R. Cao, J.-W. Zhao, L.-R. Wen, Y.-J. Liu, Y.-M. Xia and S.-Z. Zhu, *Tetrahedron Lett.*, 2009, **50**, 6247; (*c*) X.-J. Mu, J.-P. Zou, R.-S. Zeng and J.-C. Wu, *Tetrahedron Lett.*, 2005, **46**, 4345.

2 (*a*) H.-Z. Li, W.-J. Xue and A.-X. Wu, *Tetrahedron*, 2014, **70**, 4645; (*b*) T. B. Nguyen and P. Retailleau, *Green Chem.*, 2017, **19**, 5371; (*c*) L. Gan, Y. Gao, L. Wei and J.-P. Wan, *J. Org. Chem.*, 2019, **84**, 1064; (*d*) P. Yu, Y. Wang, Z. Zeng and Y. Chen, *J. Org. Chem.*, 2019, **84**, 14883; (*e*) Z. Wang, H. Xie, F. Xiao, Y. Guo, H. Huang and G.-J. Deng, *Eur. J. Org. Chem.*, 2017, 1604.

3 For recent reviews, see: (*a*) T. B. Nguyen, *Adv. Synth. Catal.*, 2020, **362**, 3448; (*b*) S. Liu, G.-J. Deng and H. Huang, *Synlett*, DOI: 10.1055/s-0040-1707217.

4 (*a*) T. B. Nguyen, M. Q. Tran, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2014, **16**, 310; (*b*) T. B. Nguyen, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2012, **14**, 4274.

5 (*a*) N. T. Do, K. M. Tran, H. T. Phan, T. A. To, T. T. Nguyen and N. T. S. Phan, *Org. Biomol. Chem.*, 2019, **17**, 8987; (*b*) T. H. Ho, H. H. K. Le, T. A. To, T. T. Nguyen and N. T. S. Phan, *Bull. Chem. Soc. Jpn.*, 2020, **93**, 783.

6 For selected examples, see: (*a*) J. -R. Zhang, L. -Z. Zhan, L. Wei, Y. -Y. Ning, X. -L. Zhong, J. -X. Lai, L. Xu and R. -Y. Tang, *Adv. Synth. Catal.*, 2018, **360**, 533; (*b*) J.-C. Deng, Y.-C. Gao, Z. Zhu, L. Xu, Z.-D. Li and R.-Y. Tang, *Org. Lett.*, 2019, **21**, 545; (*c*) T. Guo, X.-N. Wei, M. Zhang, Y. Liu, L.-M. Zhu and Y.-H. Zhao, *Chem. Commun.*, 2020, **56**, 5751.

7 For selected reviews, see: (*a*) L. M. Ramos, M. O. Rodrigues and B. A. D. Neto, *Org. Biomol. Chem.*, 2019, **17**, 7260; (*b*) S. Zhi, X. Ma and W. Zhang, *Org. Biomol. Chem.*, 2019, **17**, 7632. Recent examples:; (*c*) S. Shi, P. Zhang, C. Luo, S. Zhuo, Y. Zhang, G. Tang and Y. Zhao, *Org. Lett.*, 2020, **22**, 1760; (*d*) R. Semwal, C. Ravi, S. Saxena and S. Adimurthy, *J. Org. Chem.*, 2019, **84**, 14151.

8 (*a*) D. L. Priebbenow and C. Bolm, *Chem. Soc. Rev.*, 2013, **42**, 7870; (*b*) K. Okamoto, T. Yamamoto and T. Kanbara, *Synlett*, 2007, **17**, 2687.

9 An independent synthesis of intermediate **7** will be attempted.

10 For a consideration of such the sulfur attack to imine, see: W.-J. Xue, Y.-Q. Guo, F.-F. Gao, H.-Z. Li and A.-X. Wu, *Org. Lett.*, 2013, **15**, 890.

