

COMMENT

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Comment on “Dithiocarbamate-mediated thioamidation of arylglyoxylic acids by decarboxylative–decarbonylative C–C bond formation reactions” by D. Patra and A. Saha, *Org. Chem. Front.*, 2023, 10, 1686

Xavier Creary

The reported thioamidation reaction of phenylglyoxylic acid, PhCOCO_2H , gives only a 5% yield of thioamide product, and not the 96% yield reported in *Org. Chem. Front.*, 2023, **10**, 1686. The proposed Pd(II) catalyst plays no role in the reaction. Labelled phenylglyoxylic acid, $\text{Ph}^{13}\text{COCO}_2\text{H}$, gave a thioamide product where the ^{13}C label is retained. This rules out the suggested mechanism, which involves a phenyl radical derived from decarbonylation of benzoyl radical.

Introduction

This Comment concerns a paper by Debabrata Patra and Amit Saha that appeared in *Org. Chem. Front.*, 2023, **10**, 1686, in which a variety of thioamides are synthesized by a palladium catalyzed reaction of arylglyoxylic acids, dithiocarbamates, and ammonium persulfate (Scheme 1). Complex reactions that involve phenyl radicals are reported that give over 90% yields. Facile decarbonylation reactions of benzoyl radicals are reported, despite the lack of observation of decarbonylation in numerous literature reports on this well-studied radical. Elemental sulfur is isolated by simple filtration from a reaction mixture. For these and other reasons, attempts have been made to repeat some of the unexpected claims in this paper.

Results and discussion

The main reaction described in this paper, *i.e.*, the reaction of phenylglyoxylic acid, piperidine dithiocarbamate salt, and ammonium persulfate catalyzed by $(\text{dppf})\text{PdCl}_2$ ¹ has been repeated using the conditions given in *Org. Chem. Front.*, 2023, **10**, 1686. The reaction turns black and gives a very complex mixture in which the major product is benzaldehyde. The ^1H NMR spectrum of the crude product is shown in Fig. 1. Only on very careful examination of the expanded spectrum can one see a trace of what could be the thioamide **3**. This hardly represents a 96% yield of thioamide **3**, as claimed by Patra and

Saha. The reaction was then repeated using PdCl_2 as the putative catalyst, and the results are similar. Benzaldehyde is the major product. Again, careful examination of the expanded spectrum reveals a possible trace of the thioamide **3** (not 65% as claimed in the paper).

The reaction can best be summarized in Scheme 2. For comparison purposes, and to aid in the detection of the expected product, the ^1H NMR spectrum of a pure sample of the thioamide **3** prepared by a known method² is shown in Fig. 2.

Next, the reaction was carried out a third time, *but no Pd catalyst was added*. The results mirror the reactions carried out with $(\text{dppf})\text{PdCl}_2$ or with PdCl_2 added. In other words, the proposed palladium catalyst has no impact on the small amount of thioamide **3** that is produced. In this case, the product thioamide **3** was isolated by chromatography using silica gel. The actual yield of **3** is 5%. This result is summarized in Scheme 3 and in Fig. 3.

In order to determine the origin of the small amount of thioamide **3**, the ^{13}C labelled phenylglyoxylic acid, **2*** (99% ^{13}C) was prepared.³ The reaction was then carried out using this labelled substrate **2***. The 5% thioamide product was then isolated by silica gel chromatography. ^1H and ^{13}C NMR analyses (Fig. 4 and 5) show that the product is $\text{Ph}^{13}\text{CSN}(\text{CH}_2)_5$, **3***, where the label has been retained in the product (Scheme 4). As summarized in Scheme 5, this completely rules out the mechanistic process claimed by the authors in *Org. Chem. Front.*, 2023, **10**, 1686. There is no phenyl radical involved in the reaction and neither is the potential palladium catalyst involved. While the origin of a product formed in only 5% yield is of some limited interest, clearly the product yields

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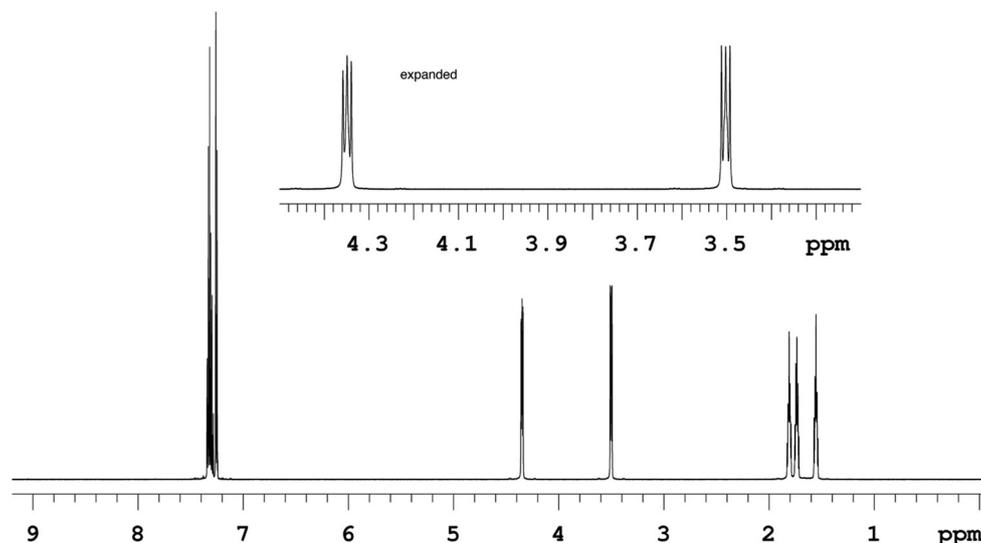
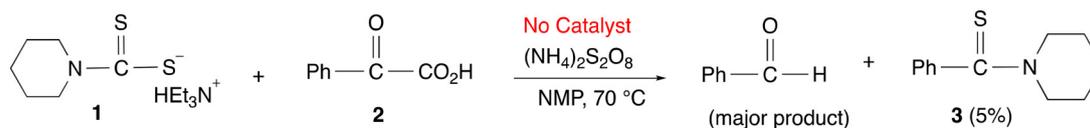


Fig. 2 ^1H NMR spectrum (CDCl_3 ; 600 MHz) of an authentic sample of thioamide 3.



Scheme 3 Observed products from attempted thioamide synthesis with no Pd(II).

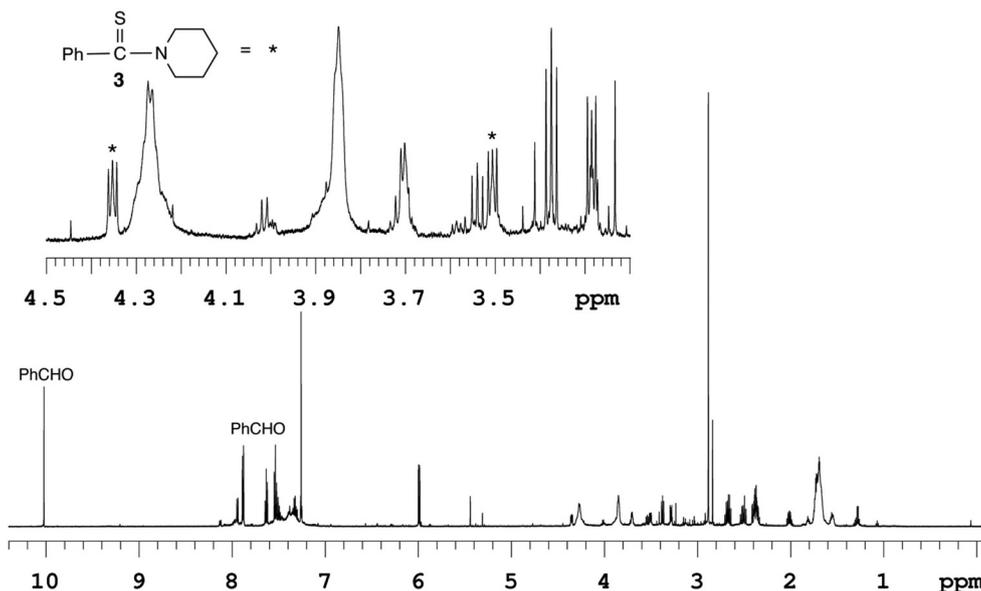


Fig. 3 ^1H NMR spectrum (CDCl_3 ; 600 MHz) of the crude products formed in the reaction of thiocarbamate salt 1, phenylglyoxylic acid, 2, and ammonium persulfate at 70 °C. No Pd catalyst was added.

Benzaldehyde is readily converted to PhCON_3 via benzoyl radicals and no decarbonylation is observed.⁸ Benzoyl radicals, when generated by other methods, add readily to electron deficient alkenes without decarbonylation.⁹ Can benzoyl rad-

icals ever undergo decarbonylation? In 1971 rates of decarbonylation were measured.¹⁰ However, the temperature was in the 341–394 °C range, consistent with Fig. 6 and 7. Only recently has it been reported¹¹ that decarbonylation of benzoyl



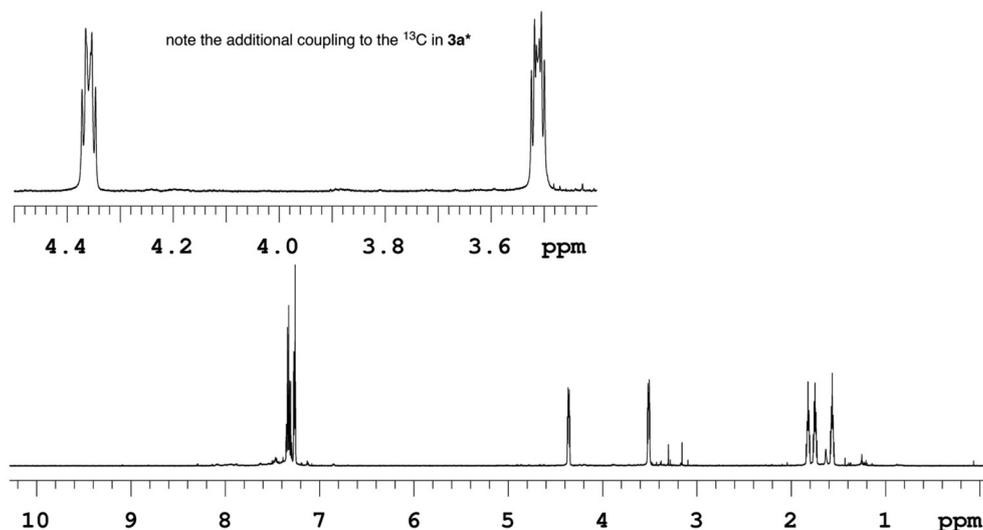


Fig. 4 ^1H NMR spectrum (CDCl_3 ; 600 MHz) of the thioamide 3^* isolated from the reaction of thiocarbamate salt 1 , $\text{Ph}^{13}\text{COCO}_2\text{H}$, 2^* , and ammonium persulfate at 70°C .

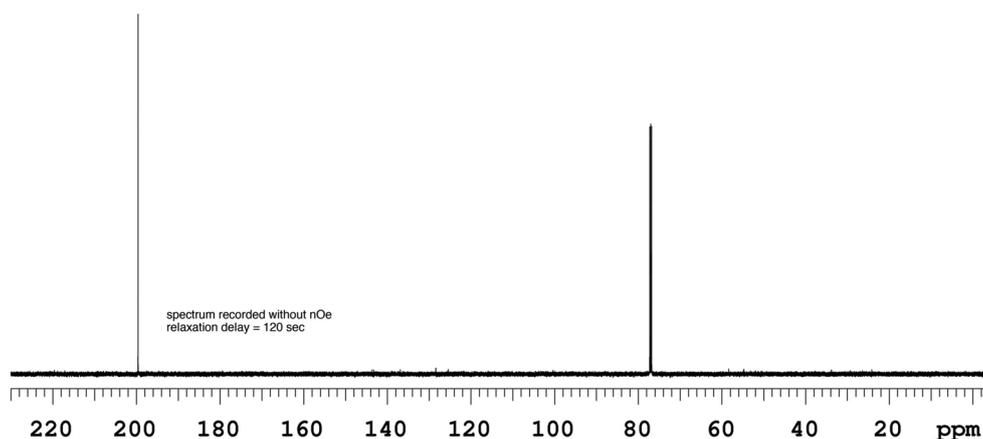
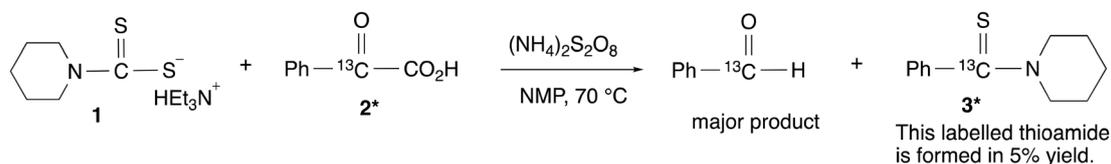


Fig. 5 ^{13}C NMR spectrum (CDCl_3 ; 150 MHz) of the thioamide 3^* isolated from the reaction of thiocarbamate salt 1 , $\text{Ph}^{13}\text{COCO}_2\text{H}$, 2^* , and ammonium persulfate at 70°C .



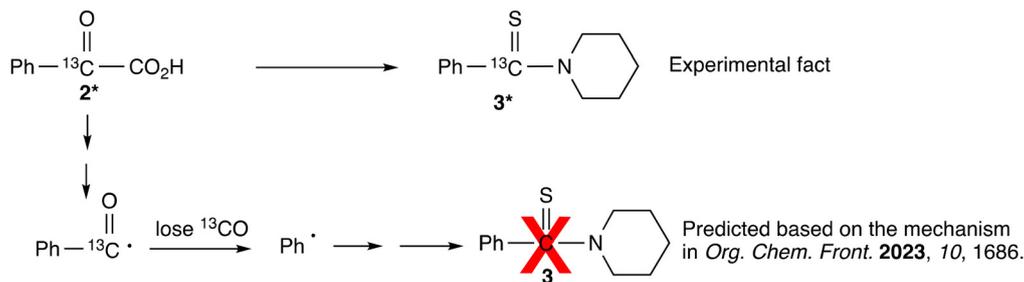
Scheme 4 Observed products from attempted thioamide synthesis with $\text{Ph}^{13}\text{COCO}_2\text{H}$.

radical 4 can occur when generated from PhCOCHO in dichloroethane at 120°C . Under these conditions it was suggested that decarbonylation generates the phenyl radical, which then adds to coumarin. Yet when benzoyl radical 4 is generated from PhCOCO_2H in dichloroethane, there is no decarbonylation

before 4 adds to coumarin. These findings are quite inconsistent and suggest that the mechanism for formation of 3-phenylcoumarin needs to be reevaluated.¹²

Decarbonylation of benzoyl radical 4 contrasts with decarboxylation of benzoyloxy radical 8 . Results of computational





Scheme 5 Mechanistic proposal disproved by labelling study.

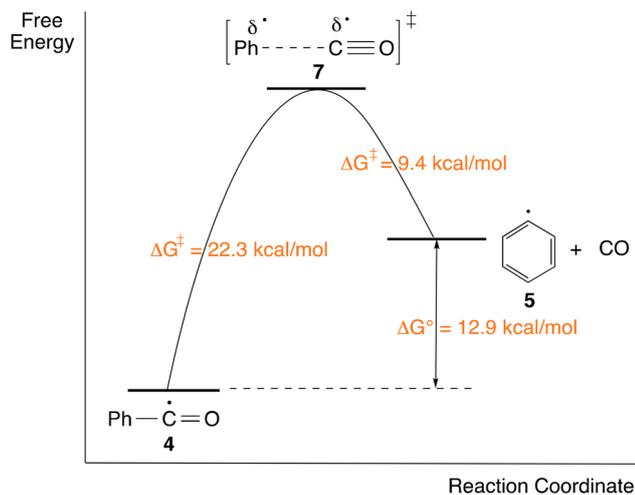


Fig. 6 M062X/6-311+G** free energy diagram for decarbonylation.

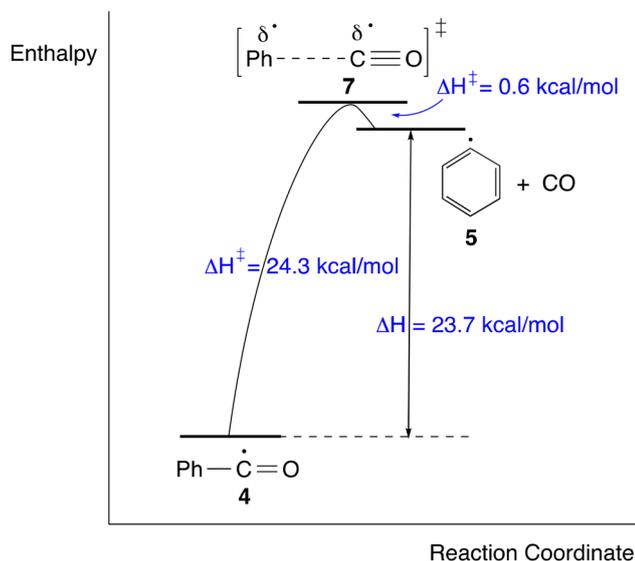
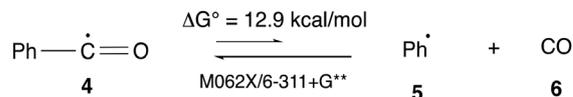
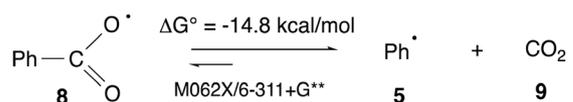


Fig. 7 M062X/6-311+G** calculated enthalpy diagram for decarbonylation.

studies are shown in Scheme 7.¹³ Computationally, decarboxylation of **8** is very exergonic ($\Delta G^\circ = -14.8 \text{ kcal mol}^{-1}$). This accounts for the fact that decarboxylation of **8** is a well-known



Scheme 6 M062X/6-311+G** calculated free energy for decarbonylation of benzoyl radical **4**.



Scheme 7 M062X/6-311+G** calculated free energy for decarboxylation of benzoyloxy radical **8**.

experimental phenomenon. The intrinsic stability of CO₂ is undoubtedly the reason for the differing behaviors of **4** and **8**.

Conclusions

Given all of the findings described in this Comment, I now conclude that there are numerous issues in *Org. Chem. Front.*, **2023**, *10*, 1686 that need to be addressed. The product yield of **3** in the reaction of phenylglyoxylic acid is only about 5% (not 96%). Without adding any Pd catalyst, the 5% yield of **3** suggests that the palladium species is not involved in the formation of this trace amount of product. The mechanism for formation of **3** does not involve phenyl radical, as shown by a labelling study, and there is no evidence of decarbonylation. This suggests that the putative mechanism given in Scheme 5 of *Org. Chem. Front.*, **2023**, *10*, 1686 is incorrect. Finally, the reaction turns very dark (black) at the end and there is no formation of elemental sulfur as shown in Fig. 1 of the paper.

As a final remark, reaction mechanisms are never absolutely proven and hence can often be up for debate. However, factual experimental results are not open for debate or interpretation. Since the reagents used in the experiments are available in most organic laboratories, or commercially available, others are encouraged to verify the experimental facts concerning the reactions discussed.

Conflicts of interest

There are no conflicts of interest to declare.



Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures and computational details. See DOI: <https://doi.org/10.1039/d4qo00393d>.

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