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Oxidative N–N Bond Formation Versus the Curtius Rearrangement

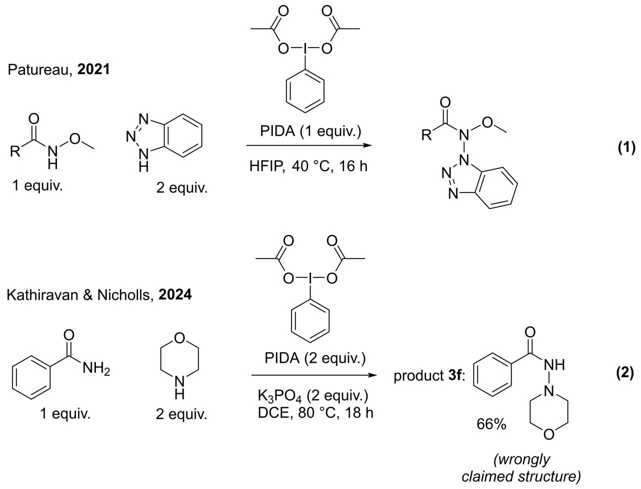
Melissa Hohenadel,[a] Ben Ebel,[a] Iris M. Oppel,*[a] and Frederic W. Patureau*[a]

The oxidative formation of N–N bonds from primary amides has been recently reported and then retracted in the journal *Nature Communications* by Kathiravan, Nicholls, and co-authors, utilizing a hypervalent iodane reagent. Unfortunately, the authors failed to recognize the Curtius reaction taking place under the described reaction conditions. Thus, the claimed N–N coupling products were not formed. Instead, the Curtius rearrangement urea coupling products were obtained. We demonstrate this herein by means of NMR and x-ray analysis, as well as with the support of an alternative synthetic route.

Introduction

Cross dehydrogenative N–N coupling reactions are particularly desirable due to the presence of N–N bonds in numerous important organic scaffolds on the one hand, and the attractive step and atom economy usually associated to such and related methods on the other.[1–11] These types of reactions are, however, particularly challenging, due to the high electronegativity of nitrogen as well as the many possible side reactions, which can occur with organic amines under strong oxidative conditions.

In March 2024, Kathiravan, Nicholls and co-authors reported in the journal *Nature Communications* a method claiming to enable the cross dehydrogenative N–N coupling of primary benzamides with simple secondary amines, under the action of PIDA (diacetoxyiodobenzene).[12] In the present contribution, we present and discuss some of the experimental evidence that we obtained while trying to reproduce the results of Kathiravan & Nicholls, which eventually led to a full retraction of the article in June 2024.[12] Their reaction conditions are inspired from a previous report from our group from 2021, which featured the cross dehydrogenative N–N coupling of *secondary N*-methoxy amides with benzotriazoles, likewise under the action of PIDA (Scheme 1, Parts (1) and (2)).[13] We were originally quite excited by this new development, as the reaction scope of Kathiravan and Nicholls seemed considerably broader compared to our anterior report, through the simple addition of a base (K_3PO_4). As soon as it appeared online, we therefore sought to study it, starting with reproducing the key results.



Scheme 1. Intermolecular cross dehydrogenative N–N coupling with PIDA.

Results and Discussion

Thus, we focused on the simple oxidative coupling of primary benzamide **1f** with morpholine **2**, which delivers product **3f**. (We adopted the product numbering of Kathiravan, Nicholls and co-authors, for the sake of simplicity).[12] Their reported isolated yield could indeed be reproduced using the described method (66% versus 66%, Scheme 2). Moreover, the collected ^{1}H and ^{13}C NMR spectra were found to correspond to that of Kathiravan and Nicholls, with high fidelity. Upon closer inspection, however, it occurred to us that the N–N benzamide coupling products claimed by them would feature very similar lines with the hypothetical urea structures, which would arise from the well-known[14] Curtius rearrangement (Scheme 2, Part (1)). Indeed, the two structures, the claimed N–N–CO coupled product, and the Curtius N–CO–N rearranged product are magnetically similar, and moreover have the same exact mass. We thus decided to experimentally investigate the possibility that the product structures proposed by Kathiravan, Nicholls and co-authors might be wrong.

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[a] *M. Hohenadel, B. Ebel, I. M. Oppel, F. W. Patureau*
Institutes of Organic and Inorganic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
E-mail: iris.oppel@ac.rwth-aachen.de
frederic.patureau@rwth-aachen.de
Homepage: https://www.patureau-oc-rwth-aachen.de/

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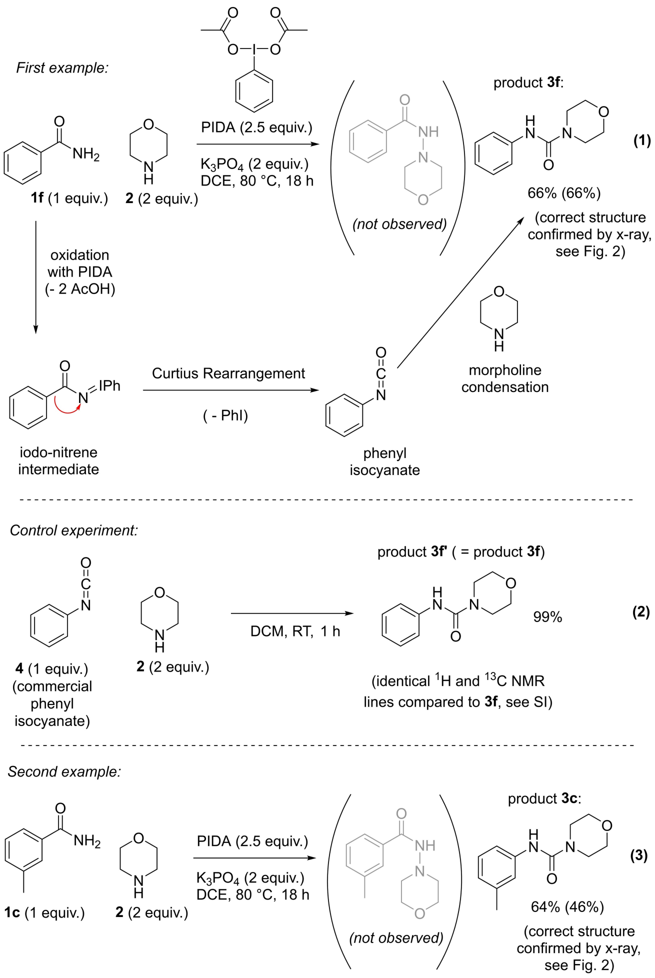

Scheme 2. Oxidative N–N bond formation versus the Curtius rearrangement, isolated yields. Yields in parentheses are the original ones reported by Kathiravan, Nicholls and co-authors.[12]

Therefore, we first decided to access the alleged N–CO–N urea product through a different synthetic route, in order to compare it to that claimed by Kathiravan and Nicholls. Commercial phenyl isocyanate (**4**), a chemical with which we have experience from a recent publication,[15] was thus united with morpholine in DCM at RT for an hour. This afforded urea product **3f'** in impressive 99% isolated yield (Scheme 2, Part (2)). Strikingly, both the ^{1}H and ^{13}C NMR spectra of **3f'** were found identical to the ones obtained by reproducing the method of Kathiravan and Nicholls, and indeed to their own reported spectra (Figure 1). Next, we mixed the two products, **3f** and **3f'**, obtained by the two different routes, in a 1 : 1 ratio, and then re-performed ^{1}H and ^{13}C NMR analysis of the mixture (see SI). Only a single set of lines were thus obtained, proving that the two routes lead to the exact same product (**3f** = **3f'**), which is the Curtius urea. Finally, we were fortunate enough to grow suitable crystals of product **3f**, obtained with the Kathiravan and Nicholls method, for x-ray analysis, from slow diffusion of pentane into a dichloromethane solution. There too, the urea structure was unambiguously confirmed (Figure 2). Finally, for good measure, we reproduced a second example of Kathiravan, Nicholls, and co-authors, starting from benzamide **1c** (*meta*-methyl-benzamide). Product **3c** was thus obtained in 63% isolated yield (Scheme 2, Part (3)), which is even a bit higher than reported (46%).[12] There too, suitable crystals could be grown, and an x-ray structure again confirmed the Curtius rearranged urea product (Figure 2).[16]

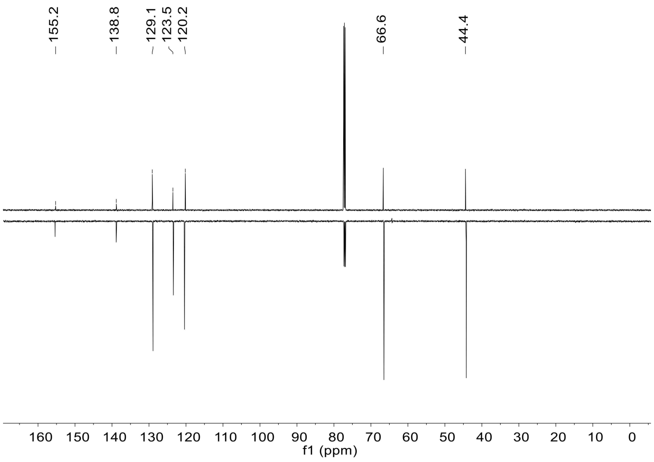

Figure 1. ^{13}C NMR spectrum of product **3f** obtained by the Kathiravan and Nicholls method ($CDCl_3$, top), and ^{13}C NMR spectrum of the product obtained from the reaction of phenyl isocyanate **4** with morpholine **2** (**3f'** = **3f**, $CDCl_3$, beneath), see SI.

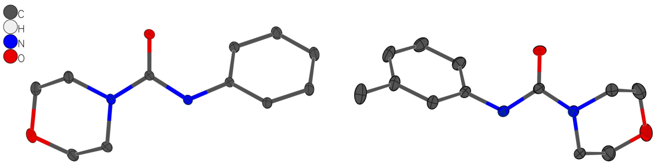

Figure 2. X-ray structure of **3f** (CCDC-2346659, left) and **3c** (CCDC-2346658, right). ADPs are scaled to 70% probability. Compound **3f** crystallizes in the monoclinic space group *P2₁/c* with *Z* = 4, and compound **3c** in the orthorhombic space group *Pna2₁* with *Z* = 8. H–atoms were omitted for clarity.

Conclusions

In conclusion, we demonstrated in this short report that the recently reported method by Kathiravan, Nicholls and co-authors does not furnish the claimed N–N coupled products, but rather the long known Curtius rearrangement urea products. The reaction most likely proceeds through a hypervalent nitrene-iodane intermediate (Scheme 2), which is formed due to the *primary* amide character of the substrate, in contrast to our previous method with *secondary* amides for which nitrene formation is blocked by the *N*-methoxy functional group. We hope that this case reminds synthetic method developers and beyond to always adopt a critical attitude towards exciting new results, in particular regarding structural interpretation.

Supporting Information Summary

Experimental section including characterization data and NMR spectra. The authors have cited additional references within the Supporting Information.[17–23] CCDC deposition numbers: 2346659 (for **3 f**), and 2346658 (for **3 c**), contain the supplementary crystallographic data. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service. https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202402355

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cross dehydrogenative coupling · Oxidative N–N bond formation · PIDA · Benzamide · Curtius rearrangement

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