Selective synthesis of six products from single indolyl α-diazocarbonyl precursors via catalyst variation

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**Abstract:** Indolyl α-diazocarbonyls can be selectively cyclised to give six distinct products through the careful choice of catalyst and reaction conditions. A range of catalysts were used, including complexes of Rh(II), Pd(II) and Cu(II), as well as SiO2, to promote diazo decomposition and subsequent cyclisation/ rearrangement via a range of mechanistic pathways.

The ability to access structurally diverse compounds for biological screening is the cornerstone of lead generation in the pharmaceutical and agrochemical industries.[1] In most cases, such compounds are generated using organic synthesis, and over the years, a number of reliable and predictable synthetic methods have emerged.[1,2] The importance of such methods cannot be over-stated, but nonetheless, there is also value in the examination of reaction systems that react less predictably.[3] Reactive precursors that are known to participate in a wide range of synthetic transformations can significantly streamline the synthesis of diverse compounds by allowing multiple products to be generated from single precursors, providing their reactivity can be controlled.

With this in mind, we initiated the research described herein, focusing on the reactions of indolyl α-diazocarbonyl compounds.[4] The utility of diazo-precursors in diversity-orientated synthesis was elegantly demonstrated by Warriner and Nelson in 2014,[3] who exploited the unpredictable reactivity of α-diazoamides to generate product mixtures for bioassay. In our research we have taken an alternative approach, using a different reaction system, and focusing on controlling the ‘unpredictable’ nature of diazocarbonyl reactivity via catalyst variation. The ability to access several distinct products from a common precursor issynthetically important, and such research can also lead to advances in the study of catalysis and mechanism. With this as motivation, we challenged ourselves to uncover a reaction system capable of delivering as many product scaffolds as possible from a single precursor by varying the catalyst and reaction conditions.[5] Most reported methods of this type allow the selective synthesis of two distinct products,[6] with protocols able to deliver three or more products being much rarer.[7] However, herein we report the catalyst-selective synthesis of *six structurally distinct cyclic scaffolds* from single, α-diazocarbonyls of the form **1** via a series of mild Rh(II)-, Pd(II)-, Cu(II)- and SiO2-catalysed processes, discovered through a mixture of careful reaction design and serendipity (Figure 1).



**Figure 1.** Catalyst-selective synthesis: six scaffolds from one precursor.

Our studies began with the three step synthesis of α-diazocarbonyl **1a**, from commercially available acid **2a** (Table 1),[8] which was then treated with a range of potential catalysts (10 mol%) in CH2Cl2 at RT for 16 h. Selected results are given in Table 1 (for full details, see the Supporting Information).

**Table 1.** Initial catalyst screening.



|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Entry** | | **Catalyst[a]** | **Proportion [%][b]** | | | | | |
| **1a** | **3a** | **4a** | **5a** | **6a** | **7a** |
| 1 | **mix** | Rh2(OAc)4 | - | - | 50 | 20 | 15 | 15 |
| 2 | Rh2esp2 | - | 10 | 55 | 15 | - | 20 |
| 3 | Cu(MeCN)4OTf | - | 20 | - | 60 | 20 | - |
| 4 | Cu(MeCN)4PF6 | 15 | 65 | 20 | - | - | - |
| 5 | **A** | Rh2oct4 | - | 95 | 5 | - | - | - |
| 6 | **B** | Pd(MeCN)4(BF4)2 | - | - | - | 95 | 5 | - |
| 7 | Cu(OTf)2 | - | - | - | 70 | 30 | - |
| 8 | **C** | SiO2 (1 g/g) | - | - | - | - | - | >90 |
| [a] Reactions performed with 0.05 mmol of **2a** and 10 mol% catalyst in CH2Cl2 (0.1 M) under argon at RT for 16 h. [b] Calculated using the 1H NMR spectrum of the unpurified reaction mixture. | | | | | | | | |

A number of catalysts able to promote diazo decomposition and cyclisation were uncovered. Five identifiable products were observed in total, with products that are mechanistically related grouped to aid the subsequent discussion: spirocyclic indolenine **3a** and α,β-dicarbonyl **4a** (group **A**), C-2 annulated indole **5a** and carbazole **6a** (group **B**) and isomeric indole **7a** (group **C**). As expected, many of the catalysts afforded complex mixtures of products, exemplified by the reactions of the Rh(II)- and Cu(II)-based catalysts shown in entries 1–4 of Table 1. However, more promising catalysts were also found which enabled the selective synthesis of group **A** products **3a** and **4a** (Rh2oct4), group **B** redox isomers **5a** and **6a** [Pd(MeCN)4(BF4)2 or Cu(OTf)2] or rearrangement product **7a** (SiO2), and these catalysts were therefore selected for further optimisation.

The Rh2oct4-catalysed procedure to form **3a** was examined first. To the best of our knowledge, thisrepresents the first reported synthesis of a spirocyclic indolenine[9] from a diazocarbonyl precursor,although the C-3 C–H functionalisation of indoles using diazocarbonyl compounds has been reported,[10],[11] so this outcome was not wholly unexpected.[12] However, the formation of the oxidised product **4a** was much more surprising, with the structure of this product confirmed by X-ray crystallography.[13] Pleasingly, it was found that the selective synthesis of either product could be achieved, with the reaction outcome being dependent on the presence of air in the reaction. Thus, by switching the reaction solvent from CH2Cl2 to chloroform, reducing catalyst loading to 5 mol% and performing the reaction under oxygen-free conditions, spirocyclic indolenine **3a** was isolated in 92% yield. Furthermore, carrying out the same reaction in a flask open to air was sufficient to completely switch the selectivity, efficiently furnishing compound **4a** (Scheme 3).



**Scheme 3.** Selective synthesis of compounds **3a** and **4a**.

We propose that both reactions start with the formation of rhodium carbenoid **I**,[14] which then reacts with the nucleophilic indole via its C-3 position to form spirocyclic intermediate **II**, before undergoing protodemetallation to furnish indolenine **3a**. Then, in the presence of oxygen, we propose that indolenine **3a** forms an intermediate endoperoxide **IV**,[8a] possibly via a radical rebound process (**3a** **→** **III** → **IV**),[15] which would be expected to fragment as shown, affording product **4a** (Scheme 4).[16] Additional evidence for this mechanism (including an X-ray structure for an endoperoxide isolated from a related reaction) can be found in the Supporting Information.



**Scheme 4.** Proposed mechanism for the formation of compounds **3a** and **4a**.

While compound **4a** could be isolated in good yield, it was found to be relatively short-lived, degrading during silica gel chromatography and on storage, but pleasingly, we were able to exploit its high reactivity to deliver two new oxindole scaffolds **8a** and **9a**. Thus, two highly diastereoselective intramolecular aldol-type reactions were developed using either Brønsted acidic or basic conditions; both reactions were performed in one-pot, requiring only a solvent switch to THF and the addition of an excess of either TFA or *t*-BuOK (Scheme 5). Under acidic conditions α,β-dicarbonyl **4a** was selectively converted into *syn*-diastereoisomer **8a** in 99% yield, which we propose is a result of H-bonding between the oxindole and α,β-dicarbonyl moieties (**VII**). Conversely, under basic conditions, the *anti*-diastereoisomer **9a** was formed in good yield, which we suggest results from a reactive conformation of the form **VIII**, in which steric clashes appear to be lower than those in **VII** and the carbonyl dipoles are opposed. The structures of both productswere confirmed by X-ray crystallography.[13]



**Scheme 5.** Stereoselective formation of **8a** and **9a**.

Next, the Pd(II)- and Cu(II)-catalysed reactions were optimised, allowing the selective formation of C-2 annulated product **5a** and carbazole **6a** using either Pd(MeCN)4(BF4)2 (5 mol%) or Cu(OTf)2 (20 mol%) respectively (Scheme 6).[17],[18] A key difference between these reactions is that it is necessary to perform the carbazole-forming reaction under oxygen at 50 °C to fully promote the oxidation step. It is difficult to unambiguously determine whether these reactions proceed via direct nucleophilic attack from the indole C-2 position or via an initial C-3 attack followed by a 1,2-migration.Based on precedent for related transformations,[19] and the observation that an isolated sample of spirocycle **3a** can be converted into a mixture of compounds **5a** and **6a** upon reaction with Cu(OTf)2, we feel that the latter is more likely.



**Scheme 6.** Selective formation of products **5a** and **6a**.



**Scheme 8.** Catalyst-selective synthesis of six products from a single indolyl α-diazocarbonyl precursor (yields following isolation by column chromatography).

The silica-promoted C-2 annulation reaction required minimal deviation from the initial screen; compound **7a** was prepared in good yield by reacting diazocarbonyl **1a** with an equivalent weight of SiO2 in CH2Cl2 (Scheme 7). The reaction likely proceeds via a Wolff rearrangement induced by the mildly acidic silica[20] and trapping by the nucleophilic indole (either via direct nucleophilic attack from the indole C-2 position or via an initial C-3 attack followed by a 1,2-migration). To the best of our knowledge, only one other example of a C-2 annulation reaction of this type has been reported.[21]



**Scheme 7.** Synthesis of **7a**.

Finally, the scope of all six optimised procedures was successfully tested on five diazocarbonyl substrates (**1a-e**), delivering 30 discrete products in total (Scheme 8). Spirocycles **3a**–**e** were each formed in good yield, with variable diastereomeric ratios, which is likely due to epimerisation of the α-keto stereocentre during chromatography.The other five procedures were all well tolerated by the same precursor set; spirocyclic oxindoles **8a**–**e** and **9a**–**e**, as well C-2 annulation products **5a**–**e**, **6a**–**e** and **7a**–**e** were formed in generally good yields, which is pleasing given that no additional optimisation was performed for any of these reactions.

In summary, we report a novel catalyst-controlled approach to form six structurally diverse products from a single α-diazocarbony precursor. While other catalyst-selective synthesis systems are known,[5–8] *we know of no other capable of delivering the level of scaffold diversity as that reported herein by simply varying the catalyst and reaction conditions*. Given the importance of the various compound classes and the high diversity accessible from common precursors,the methods are expected to be of much synthetic interest,[22] while the novel reactivity and mechanistic information uncovered is also likely to be of interest to researchers studying catalysis. These discoveries (some of which were serendipitous) were made as a consequence of challenging the methodology in terms of the number of products that could be selectively formed; much as natural product synthesis has long been used to inspire the invention of new synthetic processes,[23] we believe that the same principles apply in catalyst-selective synthesis.

Acknowledgements

The authors wish to thank the University of York (M. J. J. and W. P. U.) and the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-013, W. P. U.) for financial support and Dr. A. C. Whitwood (University of York) for X-ray crystallography.

**Keywords:** α-Diazocarbonyls • Diversity • Spirocycles • Catalysis • Indoles

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