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ARTICLE TYPE

Azide trapping of metallocarbenes: generation of reactive C-acylimines and domino trapping with nucleophiles

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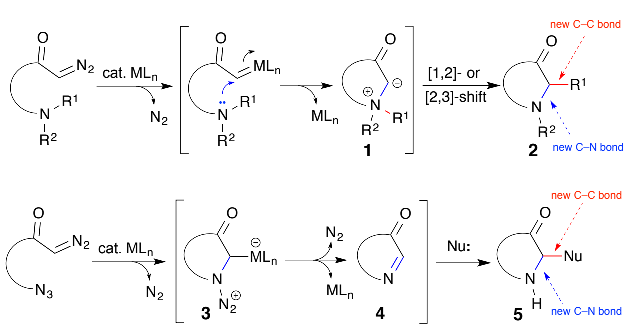
Azide-tethered diazocarbonyl compounds undergo copper-catalyzed conversion to transient C-acylimines. These reactive intermediates can be trapped with a variety of carbon nucleophiles, giving rise to complex 3-indolinone frameworks, including those with adjacent tetra-substituted carbon centres, in a single transformation.

Introduction

The generation and rearrangements of ammonium ylides offers an effective route to complex nitrogen-containing targets.[1] Particularly in the case of nitrogen heterocycles, an attractive approach involves intramolecular addition of a transient metallocarbene to a pendent tertiary amine. This process directly affords a cyclic ammonium ylide **1** which can undergo a subsequent rearrangement process (Scheme 1). Most typically this involves migration of a nitrogen substituent to the neighboring ylide carbon to give **2**.[2] Less nucleophilic amide nitrogens can also participate, though complications from competing formation of carbonyl ylides can arise.[3]

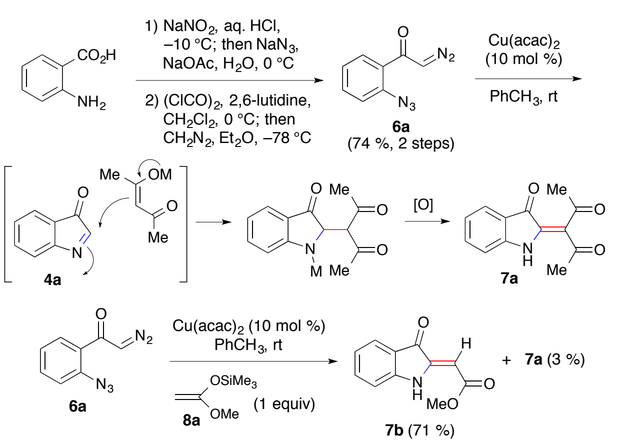
Organic azides can intercept a variety of electrophilic species in synthetically useful fashion,[4] such as aziridination of electron-deficient alkenes[5] or Schmidt rearrangement.[6] We speculated that replacement of basic amine with azide in the reaction sequence above might permit cyclization to betaine **3**, which was expected to undergo loss of dinitrogen to form cyclic *C*-acylimine **4**.[7-11] If this reaction were carried out in the presence of a suitable nucleophile, **4** could be trapped to provide adduct **5** through a domino process. With two molecules of dinitrogen as the only by-products, this transformation would also have significant potential as a green process. Herein, we report the results of our preliminary exploration of this reaction, demonstrating effective generation and trapping of the acylimine with β-dicarbonyl compounds, silyl ketene acetals, an electron-rich 1,3-diene, and *N*-methylindole.



Scheme 1 Metallocarbene trapping by nitrogen nucleophiles

Results and Discussion

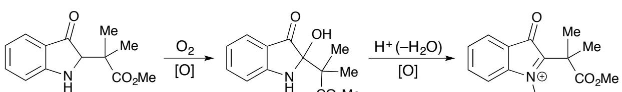
To test the viability of this hypothetical process, we required a substrate which held the diazoketone and azide moieties in close proximity, and with a molecular formula whose ratio of (carbon+oxygen) atoms to nitrogen atoms permitted safe handling.[12] Anthranilic acid-derived substrate **6a** could easily be prepared in two steps from readily available starting materials, and was amenable to handling and purification on scales of < 1 g (Scheme 2).[13] Treatment of this compound with 10 mol% $Cu(acac)_2$ in toluene at room temperature with no added nucleophile led to rapid consumption of **6a** and the formation of multiple highly coloured products. Purification of this mixture yielded small quantities of a bright red solid, which was identified as alkylideneindolone **7a**, apparently formed by nucleophilic trapping of the intermediate **4a** by the



Scheme 2 Preparation and preliminary reactions of **6a**

acetylacetonate ligand from the catalyst, followed by autoxidation of the adduct. Importantly, 3*H*-indole-3-one **4a** was not isolated in this or any subsequent experiment.[14] The ready formation of **7a** in the presence of catalytic amounts of acetylacetonate nucleophile indicates the high reactivity of this intermediate.[15] With this in mind, we carried out the same reaction, this time in the presence of 1 equiv. of silyl ketene acetal **8a**. In this case, known alkylidene indolone **7b**[16] was obtained in good yield, along with traces of **7a**. Notably, no evidence was seen for competing reaction of **8a** with the intermediate metallocarbene, indicating that intramolecular capture by azide to generate **4a** is kinetically favored.

Several other catalysts were screened, and of these copper(II) bis(hexafluoroacetylacetonate) ($Cu(hfacac)_2$) was found to give optimal results, affording product in good yield with no competing trapping by the ligand (Table 1, entry 1). A variety of traps (2 equiv.) were then examined under these conditions. To avoid potential catalyst deactivation, we focused on carbon nucleophiles as opposed to heteroatom nucleophiles that might bind tightly to the copper complex. Efficient trapping was seen with tetra-substituted silyl ketene acetal **8b**, affording indolone **7c** in excellent yield (entry 2). A dehydrogenated product analogous to **7a**,**b** could not be formed in this case due to the exocyclic quaternary centre; however, slow oxidation to a different product was observed (Scheme 3). Upon prolonged exposure to air, **7c** produced 2-hydroxyindolone **10**. Further oxidation was observed when **10** was allowed to stand in $CDCl_3$, presumably the result of elimination due to traces of acid.[17]



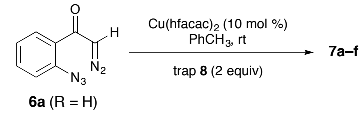
7c **10** **11**

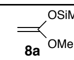
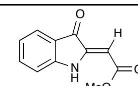
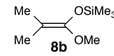
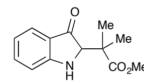
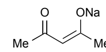
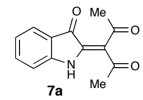
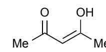
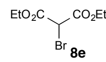
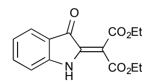
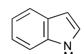
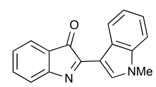
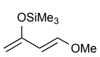
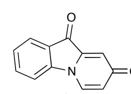
Scheme 3 Oxidation of **7c**

Deliberate inclusion of Na(acac) **8c** afforded adduct **7a** in good yield; acetyl acetone itself also provided this product, but at a disappointingly slow rate (entries 3 and 4). Alternatively, diethyl bromomalonate **8e** did afford **7d** in good yield without the need for added base (entry 5); in this case, the exocyclic alkylidene group is presumably formed via elimination rather than autoxidation. *N*-Methylindole **8f** gave known indolylindolone **7e**[18] (entry 6), and use of the Danishefsky diene **8g** led to tricyclic 4-pyridone **7f** in good yield (entry 7), presumably via stepwise Mannich/Michael process with **4a**,[19] followed by autoxidation. Trapping was also attempted using triethylsilane and phenyl boronic acid pinacol ester; however, these reactions did not yield any discernable adducts.

A second substrate **6b** bearing an additional carboxy stabilizing group was prepared via diazotransfer reaction with the keto ester **9**, which was readily accessible from the corresponding benzoic acid via the Ti-crossed-Claisen protocol reported by Tanabe and coworkers[20] (Scheme 4). This compound could also be subjected to the domino azide coupling/nucleophilic trapping process, though higher temperatures were required to consume the doubly stabilized diazo starting material (Table 2). Thus, treatment with $Cu(hfacac)_2$ in toluene at reflux in the presence of silyl ketene acetals **8a**,**b** furnished adducts **7g**,**h** (entries 1 and 2). Diminished

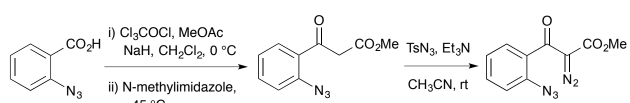
Table 1. Cyclization and trapping of diazo azides **6a** and **6b**[a]



Entry	Substrate	Nu	Product	Yield (%)[b]
1	**6a**	 **8a**	 **7b**	96
2	**6a**	 **8b**	 **7c**	93
3	**6a**	 **8c**	 **7a**	78
4	**6a**	 **8d**	**7a**	--[c]
5	**6a**	 **8e**	 **7d**	83
6	**6a**	 **8f**	 **7e**	53
7	**6a**	 **8g**	 **7f**	75

[a]Standard procedure: A solution of **6** in PhMe (0.04 M) was added dropwise over 1 h by syringe pump to a solution of $Cu(hfacac)_2$ (10 mol %) and the trap (2 equiv) in PhMe (0.04M) at rt. [b]All yields given are for isolated product after chromatographic purification. [c]Small quantities of **7a** were obtained, but yield was not determined.

yields of **7h** can be attributed to the steric demand encountered during the formation of two contiguous quaternary centres. Given the lack of hydrogens at C-2 of the indolinone ring, no autoxidation of **7g**,**h** was observed.

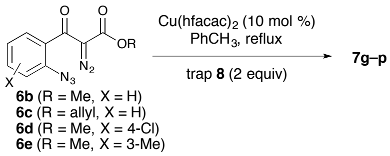


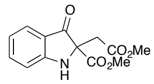
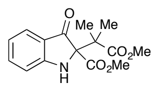
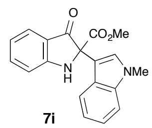
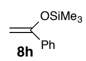
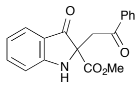
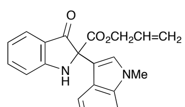
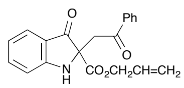
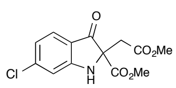
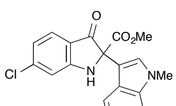
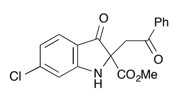
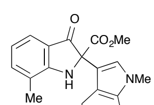
9 (68%) **6b** (quant)

Scheme 4 Preparation of distabilized substrate **6b**

Other traps were also effective (entries 3 and 4), including N-methyl indole **8f** and the trimethylsilyl enol ether of acetophenone (**8h**). The corresponding allyl ester **6c**[20] also furnished adducts, albeit in slightly diminished yields (entries 5 and 6). Interference with the intermediate metallocarbene by the pendent allyl group may contribute to yield erosion, though we were unable to detect any cyclopropane-containing impurities. The effects of ring substitution were also evaluated with substrates **6d**,**e**[21] (entries 7–10). An electron-withdrawing chloro substituent was well tolerated, affording adducts **7m–o**, as was a methyl group adjacent to the azide (**7p**). Notably, compatibility with halo substituents suggests that further elaboration of the

Table 2. Cyclization and trapping of doubly stabilized diazo azides.[a]

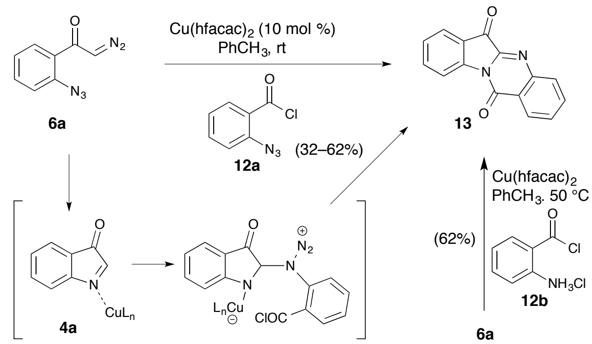


Entry	Substrate	Nu	Product	Yield (%)[b]
1	**6b**	**8a**	 **7g**	89
2	**6b**	**8b**	 **7h**	48
3	**6b**	**8f**	 **7i**	72
4	**6b**	 **8h**	 **7j**	71
5	**6c**	**8f**	 **7k**	63
6	**6c**	**8h**	 **7l**	52
7	**6d**	**8a**[c]	 **7m**	73
8	**6d**	**8f**	 **7n**	76
9	**6d**	**8h**	 **7o**	76
10	**6e**	**8h**	 **7p**	68

[a]Standard procedure: A solution of **6** in PhMe (0.04 M) was added dropwise over 1 h by syringe pump to a solution of $Cu(hfacac)_2$ (10 mol %) and the trap (2 equiv) in PhMe (0.04M) at reflux. [b]All yields given are for isolated product after chromatographic purification. [c]The OTBS silyl ketene acetal was used in place of the OTMS version.

indolinone products via cross-coupling processes should be possible.

An interesting observation was made when **6a** was treated with $Cu(hfacac)_2$ in the presence of acid chloride **12a** (Scheme 5). In this case, tetracyclic indoloquinazoline **13** was formed, albeit in variable yields. Compound **13** is the alkaloid natural product tryptanthrin,[22] whose derivatives possesses a number of promising biological activities.[23] This one-step synthesis is presumed to occur through sequential addition of the azido group of **12a** to imine **4a** (or its copper complex),[24] followed by N-acylation and elimination of dinitrogen. Consistent yields could be obtained if aniline **12b** was used in place of **12a**. In this case, an oxidation step must occur following assembly of the tetracyclic scaffold. It is notable that all trapping examples in Tables 1 and 2 involved carbon π-nucleophiles, while **12a**,**b** trapped via nitrogen. The scope of heteronucleophilic traps merits further study.



Scheme 5 Synthesis of tryptanthrin

Conclusions

Domino azide-metallocarbene coupling/nucleophilic addition has been achieved, forming substituted indolone systems by sequential formation of adjacent C–N and C–C bonds. With unsubstituted diazoketone precursors, rapid autoxidation occurs after nucleophilic trapping. A variety of nucleophiles can be used, including active methylenes, silyl ketene acetals, Danishefsky's diene, or *N*-methylindole. Use of 2-azido- or 2-aminobenzoyl chloride allows for 1-step construction of the natural product tryptanthrin. Doubly stabilized diazoketones also undergo efficient cyclization and nucleophilic capture, generating a variety of ester-substituted indolinones. Variation of ring substitution had no observable effect on the efficiency of the process. An aliphatic case also underwent coupling, but was not reactive under the usual nucleophilic trapping conditions; instead it was found that Et_2Zn trapped the imine intermediate through attack at the nitrogen atom of the C=N bond. Further studies of this process will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures and spectral data for substrates **6a-e** and adducts **7a**, **c-p**, **10**, **11**, **13**, and **19**]. See DOI: 10.1039/b000000x/

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