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Metal-mediated reactions of aryl isocyanates with dimethoxycarbene to form isatin derivatives

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ABSTRACT

Hydantoin derivatives have been established as the observed product in the reaction of aryl isocyanates with dimethoxycarbene. A change in the reactivity profile of dimethoxycarbene with aryl isocyanates was observed upon the addition of a metal species. Methodology has been developed in which the outcome of nucleophilic carbene reactions with isocyanates can be controlled with simple changes to reaction conditions.

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Nucleophilic carbenes are highly attractive species for synthesis. This can be argued based on the ability of these 1,1-dipole species to serve as carbonyl equivalents and their interesting reactivity profile.¹ However, nucleophilic carbenes have not been fully exploited as reagents in synthesis because of sometimes unpredictable reactivity and perceived difficultly in handling.

Nucleophilic carbenes have historically been accessed in synthetic applications by thermolysis of norboradienone acetals or by photolysis/thermolysis of dimethoxydiazirine precursors, which are difficult to handle.² Warkinton has developed a milder method for accessing dimethoxycarbene via thermolysis of dialk-oxy- Δ^3 -1,3,4-oxadiazolines.³ Later, a method to synthesize the bis(propylthio)carbene precursor was developed and this carbene displayed reactivity significantly different from dimethoxycarbene.⁴ With these advances the use of nucleophilic carbenes in synthesis has become more common in recent years.⁵

Nucleophilic carbenes, such as dimethoxycarbene, display a reactivity pattern very different from their electrophilic counterparts, owing to the presence of π -donating substituents that stabilize the singlet state.⁶ It is noteworthy that different species of nucleophilic carbenes can react to form complementary products. An excellent example of this variable reactivity is observed during the reaction of aryl isocyanates with either dimethoxycarbene or bis(propylthio)carbine (Fig. 1).

Aryl isocyanates react with dimethoxycarbene to form primarily hydantoin products, while bis(propylthio)carbene forms isatin derivatives.⁷

This substituent-dependent reactivity has some inherent limitations. The appropriate substitution must be built into the precursor of the nucleophilic carbene. A useful synthesis of the bis(propylthio)carbene precursor was achieved in 1998,⁴ however this precursor can be difficult to isolate due to its instability above 0 °C.

During this investigation, it was observed that a metal impurity resulted in a small yield of [4+1] cycloadduct while using dimethoxycarbene precursor. Previously, this product was only obtained when using the bis(propylthio)carbene precursor. This observation suggested the possibility of altering the reaction pathway by addition of a metal species rather than by changing the substituents on the nucleophilic carbene.

An investigation commenced to identify a suitable metal species to obtain synthetically useful yields of the [4+1] cycloadduct. Various metals were screened for optimal reactivity (Table 1) and it was found that the [4+1] adduct was obtained in small yields. Control experiments demonstrated that in the absence of the metal, the hydantoin product was obtained in the reaction of dimethoxycarbene precursor and phenyl isocyanate. This was consistent with previous reports from the literature.⁷

Ultimately, the optimal conditions used sub-stoichiometric amounts of $Cu(acac)_2/CuSO_4$ which afforded a 60% yield of the [4+1] cycloadduct. With this result in hand, the scope of the reaction was examined next.



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Figure 1. Anticipated products of phenyl isocyanate and two different nucleophilic carbene species.

Table 1

Exploration of Lewis acids to form a [4+1] product



Reagents and conditions: Reactions in toluene were performed at reflux for 4 h and reactions in chlorobenzene were performed at reflux for 1 h at 0.04 M, with 4 equiv of carbene precursor in all cases. Reagents were added and heated simultanueously.

In each case the [4+1] cycloadduct was obtained (Table 2). Activated aromatic rings produced the best yields, up to 84%. Rings with electron donating groups in non-resonance contributing positions led to yields in the 50% range. It is important to note that this class of aromatic compounds fails to provide the [4+1] cycloadduct in the absence of metal. Not surprisingly, deactivated rings resulted in low yields of [4+1]. The presence of a metal species increased the yield of the [4+1] cycloadduct in virtually every example except entry 7 (Table 2).

The most dramatic differences are seen for aromatic rings with electron-donating groups in non-resonance contributing positions (entries 5, 8, and 9). This type of aromatic ring forms [4+1] product only upon addition of the metal (Tables 2 and 3). In these cases, the products were different when no metal was present, depending on the solvent used (Table 3).

In some cases (entries 5, 8, and 9) β -lactams were observed when chlorobenzene was used as solvent. This product was recently reported by this laboratory.⁸

A very interesting example is found in example 9 which provided 54% yield of the [4+1] adduct in the metal mediated

Table 2

[4+1] cycloaddition with Cu(acac)₂/CuSO₄ in chlorobenzene



Structure	Entry	Yield A (%)	Yield B (%)	Vield C (%)	
N=C=O	1	60	0	0	
O N ₃ OMe	2	73	0	0	
O N ₃	3	73	0	0	
F ₃ C	4	20	26	0	
OMe N=C=O MeO	5	48	0	0	
MeO OMe	6	84	0	0	
O NMe ₂	7	49	0	0	
N=C=O	8	68	0	0	
MeO N=C=O	9	54	0	0	

All reactions were conducted at reflux, for 1 h at 0.04 M. See Supplementary materials for a general procedure. Acyl azides rearrange in situ to form isocyanates.

reaction, 78% yield of the hydantoin product in toluene, and 41% yield of a β -lactam product in chlorobenzene. This result was striking since three different principle products could be obtained through simple manipulations of reaction conditions.

A perplexing case is seen in entry 7 where a better yield of the [4+1] cycloaddition product was obtained in the absence of the metal. This can be explained by a potential coordination of copper to the dimethylamino nitrogen, causing the group to be less activating, as is often observed in Friedel–Craft alkylations/acylations.

Table 3

Control experiments without the catalyst in toluene and in chlorobenzene



Entry	Structure	Yield A (%) Solvent		Yield B (%) Solvent		Yield C (%) Solvent	
		a	b	a	b	a	b
1	N=C=O	0	Trace	80	60	0	0
2	Ma OMe	34	32	0	0	0	0
3	N ₃	28	49	0	0	0	0
4	F ₃ C	0	0	32	48	0	0
5	OMe N=C=O MeO	0	0	0	0	43	49 ^a
6	MeO OMe	43	52	0	0	0	0
7	NMe ₂	42	72	0	0	0	0
8	N=C=O	0	0	45	47	0	15
9	MeO N=C=O	0	0	78	Trace	0	41 ^a

All reactions were conducted at reflux for 1 h at a concentration of 0.04 M unless otherwise noted. See Supplementary materials for a general procedure.

^a These reactions were conducted at 0.01 M to increase yield of **C**, however, the yields at 0.04 M were 20% for 5 and 25% for 9.

If this were the case, the copper could serve to decrease the ability of the nitrogen group to contribute electron density to the aromatic ring.

The correlation of ring activation and product ratio led to the speculation that the most likely pathway for this reaction is electrophilic aromatic substitution. This mechanism is believed to operate in the reaction of bis(propylthio)carbene with aryl isocyanates.⁷

The role of copper in the reaction was carefully considered. As has been established in the literature, $Cu(acac)_2$ is used to catalyze urethane formation via Lewis acid activation,⁹ but it is also used to decompose diazonium species to form carbenoids.¹⁰ Other metals that also promoted formation of the [4+1] cycloadduct did little to clarify the role of copper. Rhodium(II) acetate dimer, which might be associated with carbenoid type mechanisms, promoted the reaction.¹¹ However, metals associated with Lewis acid coordination also worked, such as AlCl₃, and ZnBr₂ (Table 1). Studies were conducted to determine whether decomposition of the carbene precursor occurred at lower temperature in the presence of the metal, but no reaction took place until the normal decomposition temperature in toluene (\sim 110 °C). Attempts to isolate or trap the putative carbenoid were unsuccessful. These results. combined with careful examination of the literature led to the conclusion that, in this case, the role of $Cu(acac)_2$ was most likely that of a Lewis acid. Dimethoxycarbene is proposed to react with electrophiles to form Zwitterionic species as intemediates.^{8,12} It has also been proposed in the literature that copper preferentially coordinates to the nitrogen of an isocyanate.⁹ This coordination could increase the electrophilic nature of the isocyanate, increasing the rate of attack on the isocyanate by the nucleophilic carbene. In addition, the metal may decrease the ability of the nitrogen to participate in amide bond resonance in the presumed 1,3-dipole intermediates. This could cause the cation adjacent to the carbonyl to become more electron deficient, facilitating electrophilic aromatic substitution. The change in electronic character of the isocyanate could disfavor the pathway leading to the hydantoin product since, presumably, the nitrogen necessary for attack on the second molecule of isocyanate would be complexed with the Lewis acid.

In conclusion, new methodology has been developed using straightfoward manipulations of reaction conditions to control the outcome in the reaction of dimethoxycarbene with aryl isocyanates, allowing new access to highly substituted isatin derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 03.032.

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