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LETTERS

Rapid construction of isatin derivatives via addition of bis(alkylthio)carbenes to aryl isocyanates

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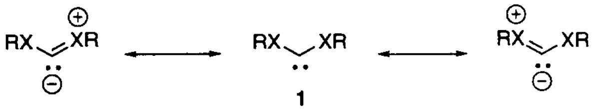
Abstract

Thermally induced cyclization between bis(alkylthio)carbenes, derived from the corresponding oxadiazolines, and substituted aryl isocyanates provides access to a variety of isatin derivatives with good efficiency. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: carbenes; cyclization; isocyanates.

Nucleophilic carbenes **1** are frequently characterized by the presence of donor substituents such as oxygen, nitrogen and sulfur that stabilize the singlet state of the reactive intermediate through conjugative donation of electron density from the heteroatoms into the vacant *p*-orbital of the carbene center (Scheme 1). A direct consequence of this orbital interaction is that these species exhibit reactivity patterns quite different from their more electrophilic counterparts.[1]



Scheme 1.

Recently, several classes of nucleophilic carbenes have been shown to be excellent reaction partners in a novel [1+4] cycloaddition pathways with vinyl isocyanates to produce highly-substituted hydroindolone products.[2] This cycloaddition protocol was subsequently shown to be a particularly effective strategy-level transformation for rapid entry into several alkaloid families,[2b,c] and chirally-modified carbene derivatives were proven to be effective reagents for delivering useful levels of asymmetric induction in the resultant hydroindolone adducts.[2a] More recently, readily accessible bis(alkylthio)carbenes were found to display interesting and preparatively useful reactivity that was, in some cases, distinct from that of the corresponding oxygen- and nitrogen-based intermediates.[3] As a rule, each of these reactions was performed in identical fashion by heating the corresponding heteroatom-substituted oxadiazoline precursors **2**[4] in the presence of the isocyanate partner to afford high yields of 2:1 adducts **3** (Scheme 2).

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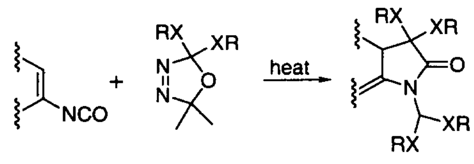
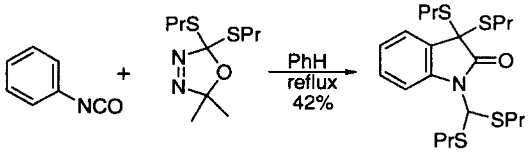


2 **3**

Scheme 2.

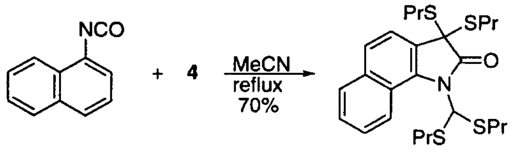
While reactive vinyl isocyanates have been quite willing participants in these reactions, the corresponding [1+4] cycloaddition process with aryl isocyanates has been observed only rarely.[5] Indeed, most reactions between nucleophilic carbenes and aryl isocyanates afford modest yields of substituted hydantoin-type products.[6] We now wish to report that bis(alkylthio)carbenes add smoothly to aryl isocyanates to afford good yields of substituted isatin products in which the ketone function emerges in protected form as a dithioacetal.[7] Thus, in a typical example, heating phenyl isocyanate with the readily available bis(*n*-propylthio)oxadiazoline **4**[3] yielded isatin **5**[8] in serviceable yield (Eq. 1).



4 **5**

(1)

The reaction appears to be quite general in nature as evidenced by the good yield of adduct **6**[8] obtained when 1-naphthyl isocyanate **7**[8] was exposed to the same carbene precursor **4** in refluxing acetonitrile (Eq. 2).



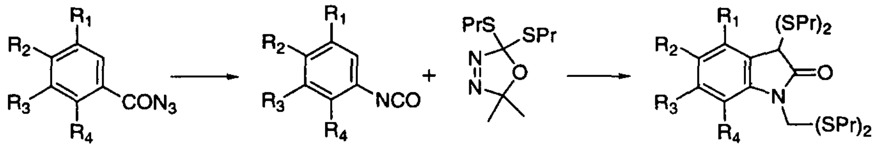
7 **6**

(2)

The scope and limitations of this process were then explored in detail and several additional examples of this novel cyclization are compiled in Table 1. Typically, an adduct is formed in these reactions that is comprised of two equivalents of carbene combined with one of the isocyanate partner, a feature which closely parallels previous observations in related transformations.[2] The second equivalent of carbene is presumed to insert into the NH bond of the initially formed isatin intermediate, and some empirical support for this putative pathway has been observed in previous studies.[3,9] Not surprisingly electron-rich arenes provided adducts in good to excellent yields, while those reactions involving electron deficient isocyanates afforded either low or no yields of isatin products (entries 6 and 8). In cases where regioisomers were possible, only one was produced, paralleling other electrophilic aromatic substitution reactions in that regard (entries 4 and 5).[10]

In summary, bis(alkylthio)carbenes have been shown to undergo a novel insertion into aryl isocyanates to produce isatin derivatives in good yields. Further work is underway in our laboratory to exploit the preparative utility of these reactions in alkaloid synthesis.

Table 1
Addition of bis(alkylathio)carbenes to aryl isocyanates



Entry	R_1	R_2	R_3	R_4	Conditions	Yield (%)[a]
1	H	MeO	H	MeO	PhH, reflux	58[b]
2	H	-O(CH$_2$)O-		H	MeCN, reflux	58[b]
3	MeO	H	MeO	H	MeCN, reflux	40[b]
4	H	H	(Me)$_2$N	H	MeCN, reflux	70[b]
5	H	H	MeO	H	MeCN, reflux	65[b]
6	H	F$_3$C	H	H	PhH, reflux	13[b]
7	MeS	H	H	Cl	MeCN, reflux	34[b,c]
8	H	NO$_2$	H	H	PhH, reflux	0

[a] All reported yields are for analytically pure, isolated products and are based on the starting acyl azide.
[b] Ref. 8. [c]A quantity of 1:1 adduct was isolated from this reaction as well.

Acknowledgements

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References

1. For leading references to nucleophilic carbenes, see: (a) Couture, P.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 1281. (b) Pole, D. L.; Sharma, P. K.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1335. (c) Arduengo III, A. J.; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *1117*, 11027. (d) Ge, C.-J.; Jefferson, E. A.; Moss, R. A. *Tetrahedron Lett.* **1993**, *34*, 7549. (e) Arduengo III, A. J.; Raiska Dias, H. V.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530. (f) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15. (g) Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443.
2. (a) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *Tetrahderon Lett.* **1999**, *40*, 2473. (b) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587. (c) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664. (d) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848.
3. Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766.
4. (a) Couture, P.; Terlouw, J. K.; Warkentin, J. *J. Am. Chem. Soc.* **1996**, *118*, 4214. (b) Kassam, K.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 5071.
5. To the best of our knowledge only one other example of this reaction has ever been observed: Er, H.-T.; Pole, D. L.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1480.
6. (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B. *Chem. Ber.* **1973**, *106*, 2174. (b) Lemal, D. M.; Gosselink, E. P.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 582. (c) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751. (d) Hoffmann, R. W.; Reiffen, M. *Chem. Ber.* **1976**, *109*, 256.
7. For other recent approaches to isatins, see: (a) Allen, D. A. *Synth. Commun.* **1999**, 447. (b) Kraynack, E. A.; Dalgard, J. E.; Gaeta, F. C. A. *Tetrahedron Lett.* **1998**, *39*, 7679. (c) Rivalle, C.; Bisagni, E. *J. Heterocyclic Chem.* **1997**, *34*, 441. (d) Methcohn, O.; Goon, S. *Tetrahedron Lett.* **1996**, *37*, 9381. (e) Hewawasam, P.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1255. (f) Ubeda, J. I.; Villacampa, M.; Auendano, C. *Synlett* **1997**, 285.
8. This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR, MS) and analytical (combustion analysis and/or HRMS) data in complete accord with the assigned structure.
9. Mechanistic studies are currently underway to shed some additional light on the details of these reaction pathways.

10. Typical procedure for the preparation of substituted isatins. General procedure for the preparation of acyl azides from the corresponding benzoic acids: A solution of the carboxylic acid in benzene (0.20 M) is treated with 1 equiv. of Et_3N and stirred for 10 min under N_2. Diphenylphosphorazidate (DPPA) (1 equiv.) is then added dropwise and the resulting reaction mixture is stirred for an additional 40 min. The solvent is removed in vacuo, and the residue is purified by flash chromatography (10:1, hexanes:Et_2O) to afford the pure acyl azide. General procedure for the additions of bis(alkylthio)carbenes to aryl isocyanates: To a two-necked round-bottom flask equipped with a reflux condenser is added a solution of the acyl azide (1 equiv.) in CH_3CN (0.1 M). The solution is heated to reflux for 0.5–1.0 h to provide the corresponding isocyanate (formation is monitored by IR). To this solution is added 2,2-bis(*n*-propylthio)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (2.5–3.0 equiv.) as a 1.0 M solution (THF) in 0.2 mL portions every 10 min. (Note: the remaining, thermally-labile oxadiazoline is stored at −78°C during the addition.) The resulting solution is refluxed for an additional 16 h at which time the solvent is removed in vacuo and the residue is purified by flash chromatography (hexanes:Et_2O; various ratios) to afford the pure adducts.