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Effect of solvent polarity on N–H insertion versus rearrangement of alkylidene carbenes

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Abstract—Alkylidene carbenes, when generated from *o*-aminobenzophenones and lithiated trimethylsilyldiazomethane, give a mixture of alkyne (by rearrangement) and indole (by N–H insertion). It has been found that this ratio of indole to acetylene shows a linear dependence on the polarity of the ethereal solvent.

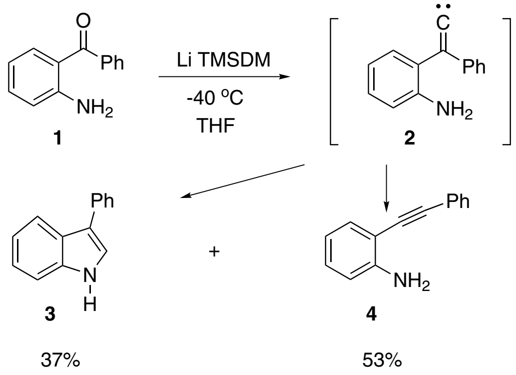
The reaction of a ketone with the lithium salt of trimethylsilyldiazomethane (TMSDM) has been shown to be an efficient way to generate the corresponding alkylidene carbene.[1–3] Using this procedure, we studied[4] the reactions of the 2,2-diaryl alkylidene carbene **2** from 2-aminobenzophenone **1**. We have observed that the ratio of the two products **3** and **4** (Scheme 1) is linearly dependent on the polarity of the reaction solvent. Our results are summarized in Table 1.[3]

Table 1. Conversions and reaction yields for Scheme 1

Entry	Solvent/E_T value[6]	% Yield	Indole/alkyne (**3/4**)
1	THF (37.4)	90	0.70
2	Glyme (38.2)	62	0.83
3	1,4-Dioxane (36.1)[a]	93	0.51
4	Et_2O (34.5)	97	0.19
5	MTBE (34.7)	82	0.41

[a] Solvent was a blend of 90% dioxane and 10% THF due to the high freezing point of pure 1,4-dioxane. The E_T value was interpolated between the two solvents.

Although, there was no discernible relationship between product ratios and the dielectric constant or dipole moment of these solvents, we found a dependence of the ndole/acetylene ratio (**3/4**) on solvent polarity as measured by the solvent solvatochromatic shift $E_T(30)$[5,6] values. Figure 1 shows a graphical representation of the product ratios versus $E_T(30)$[6] value. There was more than a fourfold change in product ratio over the solvent range studied and a seemingly linear relationship of the product ratio with solvent polarity.



Scheme 1.

There are few literature reports that deal quantitatively with carbene reactions as a function of solvent polarity. Most of these studies contend with a wide variety of possible reactions such as C–H insertion, 1,2-hydrogen shift, and alkyl/aryl rearrangement. Jones and Buck[10] report an increase in methyl migration for *tert*-butylcarbene to form 2-methyl-2-butene versus C–H insertion to form 1,1-dimethylcyclopropane as solvent polarity is increased. Gilbert and Blackburn[11] also reports increased rearrangement versus C–H insertion for the self-reaction of a 2-methyl-2-carbamoyl alkylidene carbene. Platz and Jones[12] reports no effect of solvent

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Keywords: Diphenylacetylenes; Indoles; Intramolecular N–H insertion; Carbene rearrangement; Solvent polarity.

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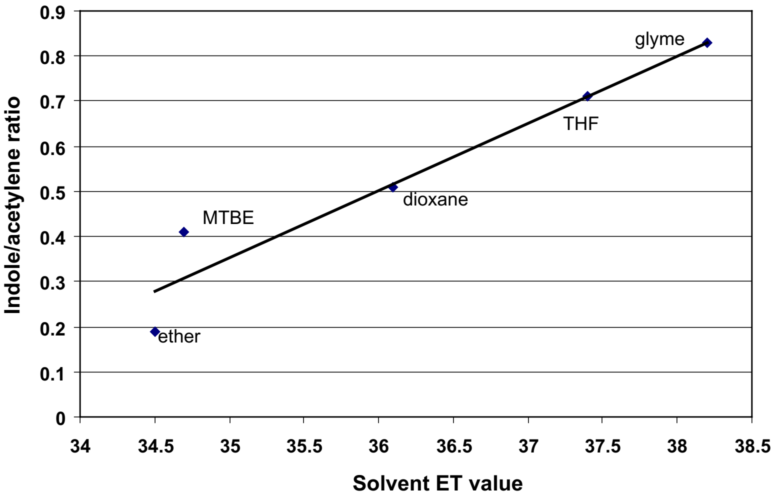
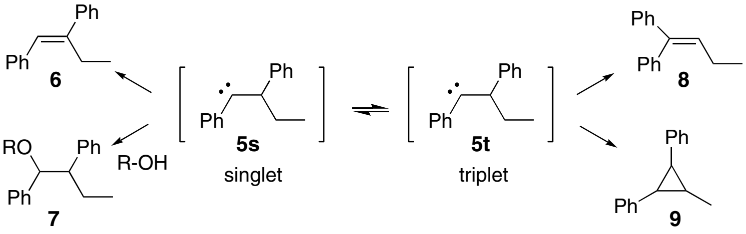


Figure 1. Plot of solvent polarity versus indole/acetylene ratio of *o*-aminobenzophenone **1**.



Scheme 2.

polarity on the reaction rate of phenylchlorocarbene with pyridine. Hadad and co-workers[13] have also investigated the effect of several solvents and substituents on the energy gap between singlet and triplet states of phenyl(carbomethoxy)carbene using time resolved IR spectroscopy. Tamioka et al.[14] reports little effect of solvent polarity (cyclohexane, benzene, and acetonitrile) on the competitive O–H insertion reaction of monophenylcarbene in MeOH/2-PrOH and MeOH/*t*-BuOH mixtures. However, he does note a very specific solvent effect on these reactions favoring MeOH O–H insertion in the presence of 1,4-dioxane (vs ether, THF, 1,3-dioxolane etc.).

The only report to quantify the effect of solvent polarity as measured by E_T values on carbene reactions is by Garcia-Garibay et al.[15] In a study focused (Scheme 2) on the reactions of 1,2-diphenylbutylene carbine he ascribed product **6** from 1,2-hydrogen shift and product **7** from intermolecular O–H insertion to the singlet state, while the triplet state led to phenyl rearrangement to give **8** and C–H insertion to give cyclopropane **9**. Grouping these reactions, he observed a linear relationship between the ratio of triplet/singlet products and solvent polarity as measured by E_T values.

We speculate that, we are observing a similar effect to that reported by Garcia-Garibay et al.[15] as the ratio of **3**:**4** increases with increasing solvent polarity. However, we think it likely that both of our products stem from the singlet carbene, and that the effect we are observing is due to a solvation-induced change in the hybridization of that carbene.

The results reported here describe a nicely balanced system where only two major reactions occur—intramolecular N–H insertion and 2,1-aryl rearrangement (without atomic labeling it is not possible to tell which aryl group migrates—phenyl or 2-aminophenyl). It may be of interest to explore the effect of aromatic substituents[16] on the selectivity of the intermediate carbene.[17]

Acknowledgement

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3. A recent publication reports a similar mixture: Miyagi, T.; Hari, Y.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 6303–6305. Aoyama and co-workers observed that the *N*-tosyl derivative of **1** was cleanly converted to the *N*-tosyl derivative of **2** when treated with lithiated TMSDM in THF.

4. Representative procedure (Table 1, entry 5). To a solution of 1.0 mmol TMSDM (0.5 mL of 2.0 M solution in hexane) in 10 mL dry MTBE at −40 °C under N_2 1.00 mmol *n*-butyl lithium (0.50 mL of 2.0 M solution in hexane) was added. This mixture was stirred and allowed to warm to 0 °C (until condensed ice melted on the outside of the flask). The solution was then cooled to −40 °C and a solution of 0.10 g (0.5 mmol) 2-aminobenzophenone in 10 mL dry MTBE was added dropwise over 1 h. The mixture was stirred at −40 °C for 2 h and then was warmed slowly to room temperature. The reaction mixture was partitioned between sequentially satd aqueous NH_4Cl and satd brine. The combined organic extract was dried ($MgSO_4$) and filtered. To this solution 50 mg of anthranilonitrile (internal standard) was added. The solution was then diluted to 100 mL with hexane for analysis by HPLC (normal phase silica, 15% MTBE in hexane eluent, UV detection at 281 nm and calibrated for response factors with anthranilonitrile internal standard). Authentic products were isolated by flash column chromatography and identities were confirmed by NMR and mp from the literature data for 3-phenyl-5-nitroindole,[7] 3-phenylindole,[8] and 2-aminodiphenylacetylene.[9]
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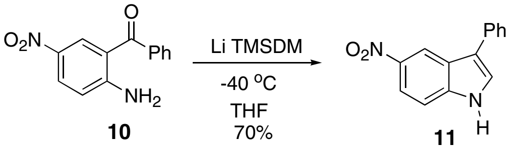

The reaction of 2-amino-5-nitrobenzophenone **10** gave only 3-phenyl-5-nitroindole **11** in 70% yield under the reaction conditions outlined above.

17. For recent reviews of indole syntheses, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075; Pindur, U.; Adam, R. J. *Heterocycl. Chem.* **1988**, *25*, 1–8.