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Influence of substitution pattern on intramolecular alkylidene carbene insertion reactions

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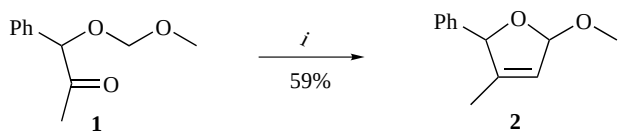
Abstract—A series of intramolecular alkylidene insertion reactions have been investigated. The nature of the substituents is demonstrated to have a dramatic effect on the outcome. In one example a novel rearrangement is observed.

Previous work[1] in our group has demonstrated that ketone **1** is a good precursor for intramolecular alkylidene carbene reactions. The carbenes may be generated in a one-step process from a ketone and, provided a five-membered product can be formed, the insertion readily takes place into conveniently activated C–H bonds (Scheme 1).[2]

We are currently examining the application of this methodology to the synthesis of a series of complex target molecules. One potential application is to the synthesis of five-membered ring sugars, which we considered might be prepared via the sequence illustrated in Scheme 2.

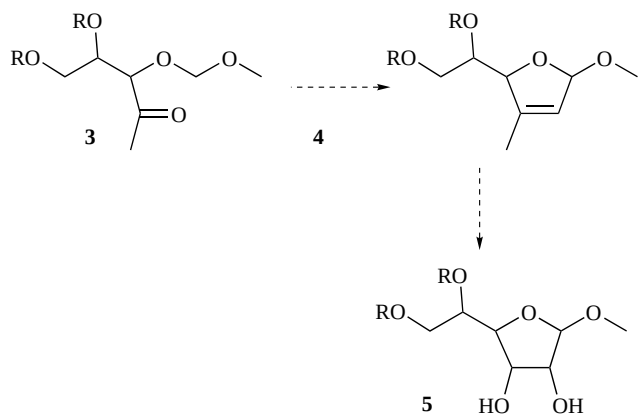
In order to examine the pivotal insertion reaction, we required a suitable synthetic approach to a series of derivatives of **3**. In the event we established that compounds **8a–d** and **9a–d** could both be synthesised via the same procedure from diol **7a–d** (Scheme 3).[3,4]



Scheme 1. *Reagents and conditions*: (i) $TMSC(H)N_2$, *n*-BuLi, DME/hexane.

It was observed that both reaction time and the amount of phosphorus pentoxide employed were crucial for the control of the ratios obtained (Table 1). The ratios quoted refer to the minimum reaction time (15 min) and lowest level of phosphorus pentoxide (15 mg/mg substrate), under which conditions appreciable amounts of **8** could be isolated. In contrast longer reaction times (ca. 1 h) coupled with the use of an excess of phosphorus pentoxide favoured product **9** (thermodynamic product) in essentially quantitative yield. It can be concluded that compound **8** is the kinetic product and an intermediate in the formation of **9**.[5]

The conversion from ester to ketone was achieved using a two-step one-pot process. An excess of Grignard reagent is required to arrive at the compounds **10a–d** and **11a–d**.[6] With a series of suitable materials in hand, we were able to examine the insertion reactions of derived alkylidene carbenes.



Scheme 2.

Keywords: alkylidene; carbene; insertion; intramolecular; rearrangement.

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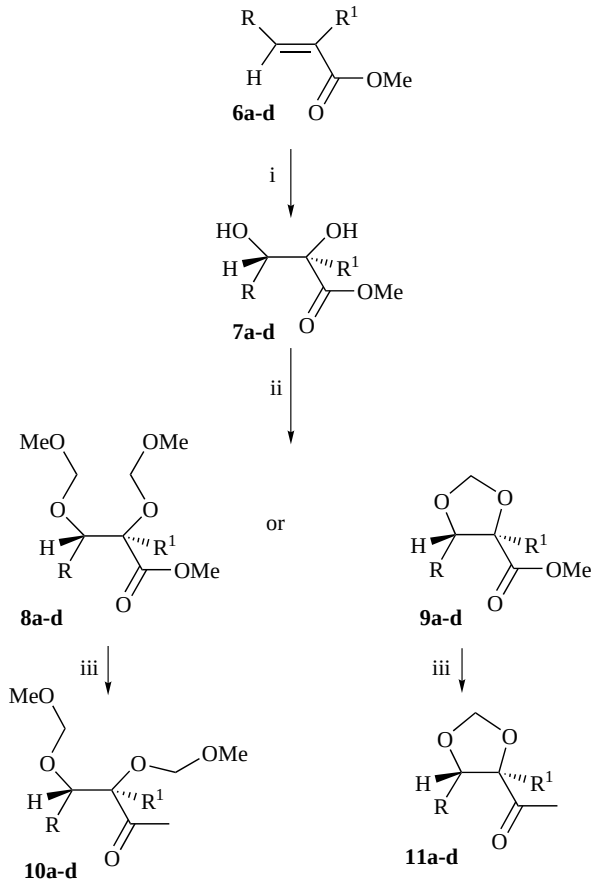


Scheme 3. *Reagents and conditions*: (i) Super Admix(α); (ii) dimethoxymethane, dichloromethane, P_2O_5; (iii) *N,O*-dimethylhydroxylamine·HCl, MeMgBr, THF.

Dihydrofurans **12** and **13** resulted from the successful insertion reactions of compounds **10a** and **10c** (Scheme 4). In the case of **12**, a product was formed as a single diastereoisomer, which has been assigned as *cis* on the basis of a positive NOE effect between the C2 and C5 protons of the dihydrofuran ring. In contrast, the attempted insertion reaction using **10b** gave a complex mixture of unidentified products (Scheme 5).

The benzyl-substituted compound **10d** also did not give any of the expected dihydrofuran products; instead compounds **14** and **15** were obtained (Scheme 6), the former as a 1:1 isomeric mixture and the latter as what appeared to be a single diastereoisomer. Product **14** is quite clearly the result of the insertion of the alkylidene carbene into the methylene group adjacent to the benzyloxy group, suggesting that this position is electronically favoured over the methoxymethyl position.

Product **15** may be formed via the insertion reaction of a carbene formed by decomposition of the diazo intermediate formed by addition of the neutral diazonium reagent to the ketone, followed by trapping by the β-methoxymethyl group, which is subsequently eliminated (Scheme 7). A C- to O-trimethylsilyl migration must also be a component of the mechanism, however, the complete process is not fully understood at present.[7]

Although we had anticipated that only the acyclic substrates **10a–d** would be likely to give insertion products, we considered it worthwhile to screen **11a** in the same reaction. As anticipated, no insertion products were obtained from this attempted reaction (Scheme 8); a complex mixture of products was formed.

There was precedent for this reaction from the work of Ohira et al. who used a C–H insertion of an alkylidene carbene in their synthesis of (−)-Neplanocin A (Scheme 9).[8] The insertion was performed on intermediate **16** to give cyclopentene **17** containing a *cis*-fused bicyclic system.

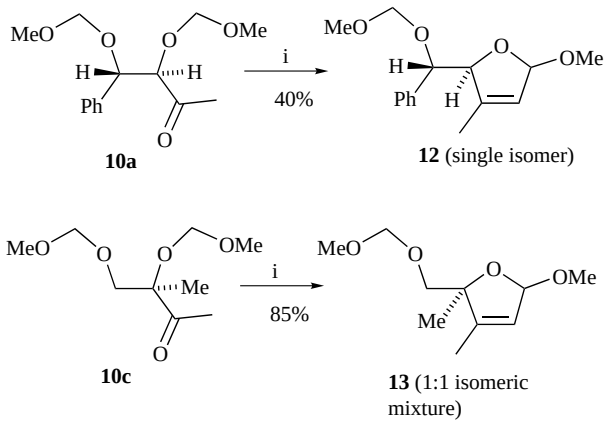
The difference can be explained by the fact that product **17** contains a readily-accessibly *cis*-ring junction, whereas the same reaction on **11d** must lead to a product bearing a *trans*-junction.
We have concluded that alkylidene carbene may be unable to reach the bridging methylene group due to the strain involved in achieving this. We did not attempt the insertion reactions of compounds **11b** and **11c**, however, we evaluated the reaction of **11d** with lithiated TMS–diazomethane in order to determine whether the carbene intermediate could react with the methylene of the benzyl protecting group to give a *trans*-fused bicyclic product. However, no insertion product was formed (Scheme 7).

In conclusion, we have demonstrated that the exact substitution pattern of a substrate has a significant effect upon the same alkylidene carbene insertion reaction. It appears that the formation of five-membered rings will always be favoured since this is a kinetic reaction, and that the C–H insertion site benefits from activation through the proximity of heteroatoms like oxygen. We intend, in the near future, to investigate further on the reasons why there is selectivity when more than one site is possible. Although we have not

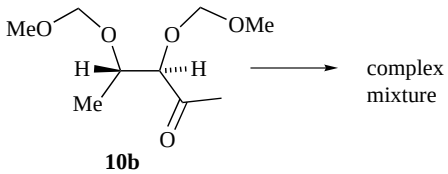
Table 1. Synthesis of substrates for insertion reactions

Series	R	R′	**7** (%)[a]	Ratio **8**:**9**[b]	**8** (%)[a]	**10** (%)[a]	**11** (%)[a]
a	Ph	H	99	4.5:1	81	62	30
b	Me	H	74	5:1	84	63	–
c	H	Me	80	3:1	57	68	–
d	CH_2OBn	H	92	3:1	56	45	26

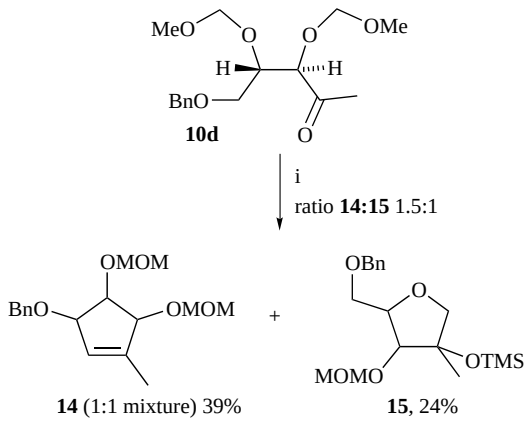
[a] Isolated yield.
[b] Under conditions of minimal time and catalyst (P_2O_5) loading.



Scheme 4. *Reagents and conditions*: (i) $TMSC(H)N_2$, *n*-BuLi, DME/hexane.



Scheme 5. *Reagents and conditions*: (i) $TMSC(H)N_2$, *n*-BuLi, DME/hexane.



Scheme 6. *Reagents and conditions*: (i) $TMSC(H)N_2$, *n*-BuLi, DME/hexane.

yet measured enantiomeric excesses of any product, the use of the Sharpless dihydroxylation in the first step permits potential access to either enantiomeric product in high e.e.

Example procedure for insertion reaction and selected spectroscopic data

Trimethylsilyldiazomethane (2.0 M in hexane, 2 equiv.) was stirred in 1,2-dimethoxyethane (20 mL/mmol of olefin) at −78°C. To this, *n*-butyllithium (2.5 M in hexane, 2 equiv.) was added carefully over 10 min. After 10 min stirring at −78°C, the cooling bath was removed and the reaction was allowed to warm until a clear solution was observed (−10°C). The reaction was cooled once again to −60°C and the ketone (1 mmol) in dimethoxyethane (20 mL) was added. The reaction was stirred for 4 h and allowed to warm to room temperature over this time. The reaction was quenched with water, extracted with EtOAc, filtered, and the combined extracts were washed with water. The residue was then dried over magnesium sulfate and concentrated in a rotavaporator. The product was purified by flash chromatography (EtOAc, hexane).

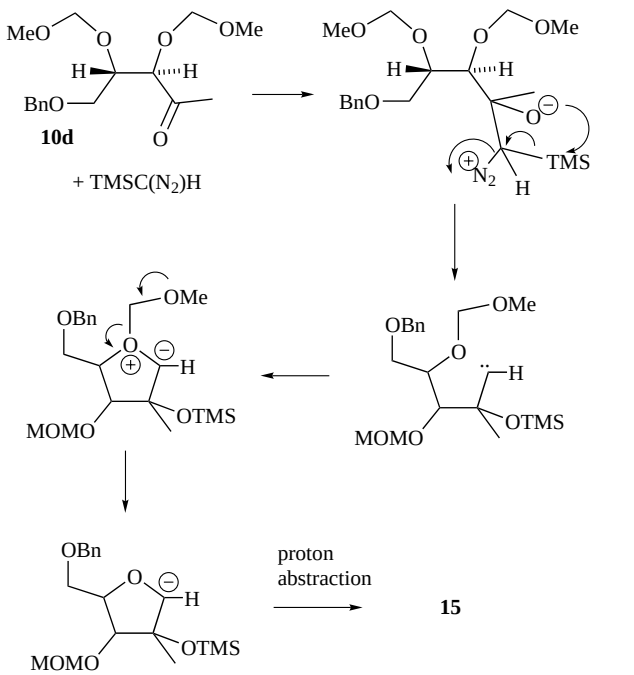
12: ν_{max} (neat)/cm^{-1} 2939, 2893, 2825, 2761, 1599, 1451, 1371, 1035, 747, 690; R_f (20% EtOAc/hex) 0.42; δ_H (300 MHz, $CDCl_3$) 7.20–7.32 (5H, m, aryl H), 5.50 (1H, d, *J* 3.9, =CH-), 5.33 (1H, s, Ph-C*H*-CH-O-), 4.88 (1H, s, -O-C*H*-OCH_3), 4.69 (1H, d, *J* 3.9, Ph-CH-C*H*-O-), 4.51 (2H, AB, J^{AB} 6.6, -O-CH_2-OCH_3), 3.29 (3H, s, -O-CH-O*CH*$_3$), 3.23 (3H, s, -O-CH_2-O*CH*$_3$), 1.67 (3H, s, -CH_3); δ_C (300 MHz, $CDCl_3$) 163.9, 143.0, 138.5, 128.6, 128.4, 128.2, 123.7, 109.1, 94.9, 89.9, 78.6, 56.1, 54.0.

13 (isomer 1): ν_{max} (neat)/cm^{-1} 2932, 2869, 1673, 1382, 1442, 1037, 844; R_f (20% EtOAc/hex) 0.33; δ_H (300 MHz, $CDCl_3$) 5.61 (1H, t, *J* 1.5, =C*H*-), 5.48 (1H, t, *J* 1.5, -O-C*H*-OCH_3), 4.64 (2H, AB, J^{AB} 7.8, -O-CH_2-OCH_3), 3.52 (2H, s, -CH_2-O-CH_2-OCH_3), 3.39 (3H, s, -OCH_3), 3.36 (3H, s, -OCH_3), 1.77 (3H, t, *J* 1.5, =C-CH_3), 1.33 (3H, s, -O-C-CH_3), δ_C (300 MHz, $CDCl_3$) 148.1, 122.1, 107.9, 97.3, 90.2, 72.1, 56.2, 54.6, 23.1, 12.5.

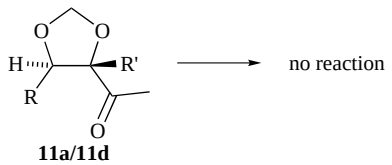
13 (isomer 2): ν_{max} (neat)/cm^{-1} 2930, 2876, 1668, 1382, 1444, 1037, 844; R_f (20% EtOAc/hex) 0.40; δ_H (300 MHz, $CDCl_3$) 5.55 (1H, t, *J* 1.5, =C*H*-), 5.47 (1H, t, *J* 1.5, -O-C*H*-OCH_3), 4.68 (2H, AB, J^{AB} 7.0, -O-CH_2-OCH_3), 3.54 (2H, AB, J^{AB} 10.2, -CH_2-O-CH_2-OCH_3), 3.40 (3H, s, -OCH_3), 3.37 (3H, s, -OCH_3), 1.79 (3H, t, *J* 1.3, =C-CH_3), 1.31 (3H, s, -O-C-CH_3); δ_C (300 MHz, $CDCl_3$) 147.2, 121.7, 107.8, 97.2, 89.8, 73.6, 55.6, 55.2, 22.3, 12.8.

14 (isomer 1): ν_{max} (neat)/cm^{-1} 2946, 2890, 2823, 2750, 1028, 919, 845, 698; R_f (20% EtOAc/hex) 0.24; δ_H (300 MHz, $CDCl_3$) 7.22–7.38 (5H, m, aryl H), 5.68 (1H, m, =CH-), 4.89 (1H, d, J^{AB} 7.5, O-CH_2-OCH_3), 4.76 (2H, s, Ph-CH_2-O-), 4.71 (1H, d, J^{AB} 7.5, O-CH_2-OCH_3), 4.54 (2H, AB, J^{AB} 15, -CH(O-CH_2-OCH_3)), 4.41–4.45 (1H, m, Ph-CH_2-O-CH-C*H*(O-CH_2-OCH_3)-), 4.07 (1H, t, *J* 6.3, -C*H*(O-CH_2-OCH_3)), 3.43 (6H, s, 2×O*CH*$_3$), 1.80–1.82 (3H, m, -CH_3); δ_C (300 MHz, $CDCl_3$) 146.3, 128.7, 128.2, 127.9, 126.3, 96.9, 96.5, 86.1, 82.7, 78.1, 70.9, 56.2, 56.1, 14.9.

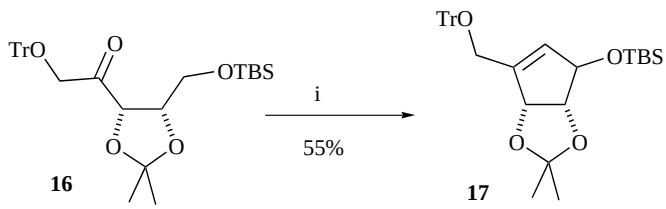
14 (isomer 2): ν_{max} (neat)/cm^{-1} 2947, 2890, 2822, 2750, 1045, 920, 844, 698; R_f (20% EtOAc/hex) 0.40; δ_H (300 MHz, $CDCl_3$) 7.25–7.39 (5H, m, aryl H), 5.59–5.63 (1H, m, =CH-), 4.85 (1H, d, J^{AB} 8.1, O-CH_2-OCH_3), 4.78 (2H, AB, J^{AB} 9.0, Ph-CH_2-O-), 4.71 (1H, d, J^{AB} 8.1, O-CH_2-OCH_3), 4.60 (2H, d, *J* 2.4, -CH(O-CH_2-OCH_3)), 4.29–4.31 (2H, m, -C*H*-C*H*(O-CH_2-OCH_3)-), 4.22 (1H, t, *J* 3.6, -C*H*(O-CH_2-OCH_3)), 3.43 (3H, s, -O*CH*$_3$), 3.42 (3H, s, -O*CH*$_3$), 1.78–1.82 (3H, m, -CH_3);



Scheme 7. Possible mechanism of formation of compound **15**.



Scheme 8. *Reagents and conditions*: (i) $TMSC(H)N_2$, *n*-BuLi, DME/hexane.



Scheme 9. *Reagents and conditions*: (i) $TMSC(H)N_2$, *n*-BuLi, THF.

δ_C (300 MHz, $CDCl_3$) 143.3, 128.7, 128.1, 127.9, 127.1, 96.4, 96.1, 88.2, 86.8, 86.2, 71.1, 56.1, 56.0, 14.7.

15: ν_{max} (neat)/cm^{-1} 2954, 2880, 2823, 1252, 1026, 920, 842, 698; R_f (20% EtOAc/hex) 0.54; δ_H (300 MHz, $CDCl_3$) 7.13–7.22 (5H, m, aryl H), 4.44 (2H, AB, J^{AB} 8.1, Ph-CH_2-O-), 4.42 (2H, AB, J^{AB} 16.2, Ph-CH_2-O-CH_2-), 4.27–4.34 (1H, td, *J* 4.5, 6.0, Ph-CH_2-O-CH_2-C*H*-O-), 3.66 (1H, d, *J* 4.2, -C*H*-O-CH_2-OCH_3), 3.58 (2H, AB, J^{AB} 10.8, -CH-O-CH_2-OCH_3), 3.50 (2H, m, -O-CH_2-C-O-Si-$(CH_3)_3$), 3.22 (3H, s, -OCH_3), 1.24 (3H, s, -CH_3), 0.00 (s, 9H, -Si-(CH_3)$_3$); δ_C (300 MHz, $CDCl_3$) 138.4, 128.7, 128.3, 128.0, 97.8, 85.3, 83.6, 80.3, 76.9, 73.9, 69.4, 56.7, 20.1, 2.5.

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