Pergamon

Tetrahedron Letters 42 (2001) 6031–6033

TETRAHEDRON LETTERS

1,6-C–H insertion of alkylidenecarbenes in 1-naphthol and 1-anthrol derivatives

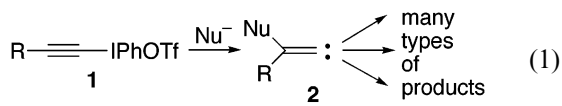
Ken S. Feldman* and Angela L. Perkins

Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA

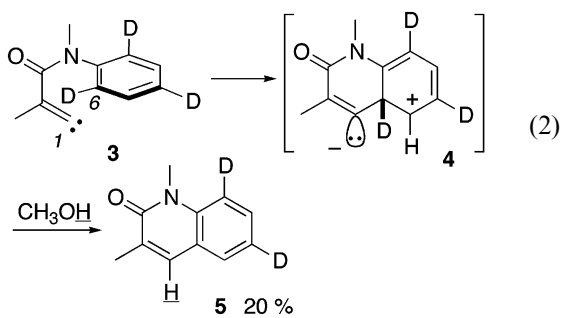
Received 6 July 2001

Abstract—Rare 1,6-C–H insertion of naphthol- and anthrol-derived alkylidenecarbenes has been observed in modest yield. Reaction in deuterated solvent did not provide any evidence in support of a reaction mechanism that requires exchange of the migrating proton with solvent. The pyran-annelated aromatic products are formed only when opportunities for the more common 1,5-C–H insertion process are blocked. © 2001 Published by Elsevier Science Ltd.

The value of alkynyliodonium salts **1** in organic transformations is, in large measure, due to their ability to serve as alkylidenecarbene **2** precursors under mild experimental conditions (Eq. (1)).[1] The alkylidenecarbenes so formed participate in a variety of distinct C–C bond forming reactions including 1,2-shift to reformulate an alkyne, alkene cycloaddition to furnish methylene cyclopropanes, heteroatom-lone pair insertion to generate reactive ylides, and most characteristically, 1,5-C(sp^3)–H insertion to deliver substituted cyclopentenes.[2] These energetic divalent carbon reagents are capable of inserting into relatively strong C(sp^2)–H bonds as well, as evidenced by annelation reactions spanning the nucleophilic heteroatom and adjacent *ortho* position of phenol, tosylanilide, or tropolone substrates.[3] On rare occasions, the products of formal 1,6-C–H insertion have been observed in the reactions of alkylidenecarbenes.[4] In the most highly scrutinized case, Gilbert's mechanistic inquiries provided evidence inconsistent with a concerted process, and a step-wise pathway featuring a zwitterionic intermediate **4** was invoked (Eq. (2)).[4a] An interest in hetero-annelated naphthalene- and anthracene-based natural products prompted an investigation of the prospects for deliberately steering an alkylidenecarbene **8** toward reaction at a site six atoms removed, either by direct 1,6-C–H insertion (**8**→**9**), or perhaps by an indirect alkene addition pathway, (**8**→**10**), Scheme 1. A recent report by Kitamura suggested that alkylidenecarbene reaction through any channel at a *peri* (e.g. 1,6) site is not likely to compete with the more energetically favorable 1,5-C–H insertion process at an available *ortho* position, (**8**→**11**, R = H).[3b] However, the fate of a carbene like **8** (R ≠ H) when the normal 1,5-C–H insertion pathway is blocked has not been described, and there is no basis at present to predict the favored reaction course between either of the scarcely precedented 1,6-C–H insertion and 1,6-alkene addition pathways. The results of 1-naphthol- and 1-anthrol-derived alkylidenecarbene reactions are reported herein. Three *ortho* substituted 1-naphthol systems **12**–**14**,[5] along with the parent 1-naphthol (**15**) for comparison and one *ortho* substituted 1-anthrol **16**,[5] were examined.



(1)



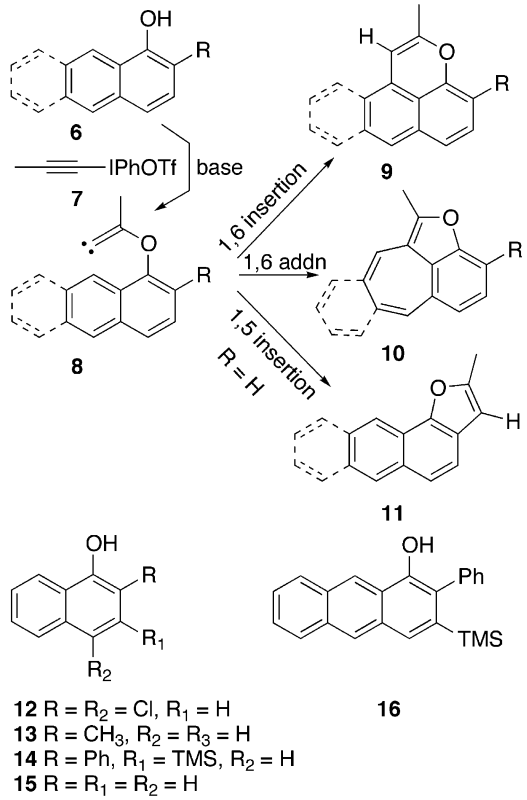
(2)

The study of 1,6-alkylidenecarbene reactivity commenced with the simple substrate 1-naphthol (**15**). This species provides a baseline for the comparison between 1,5-C–H insertion and 1,6-carbene insertion/addition

Keywords: alkynyliodonium; alkylidenecarbene; C–H insertion; *peri* position.

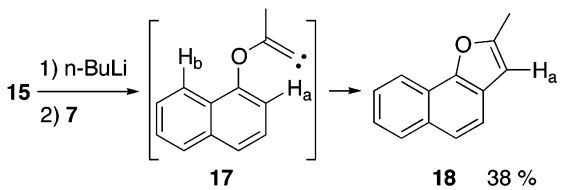
* Corresponding author. Tel.: (814)863-4654; fax: (814)863-8403; e-mail: ksf@chem.psu.edu

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01208-4



Scheme 1.

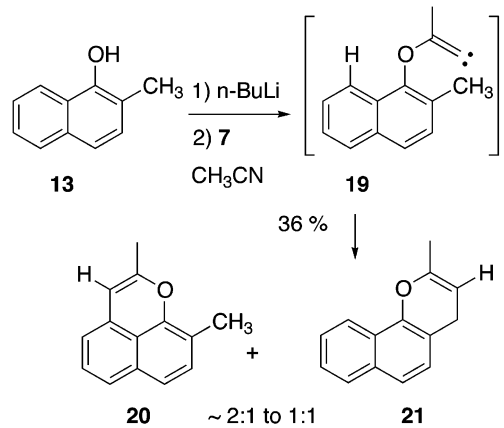
chemistry. Treatment of the anion of **15** ($LiNTMS_2$, *n*-BuLi) with test iodonium salt **7** in a variety of solvents (CH_3CN, THF, DME) afforded essentially a single product **18** in variable yield (Eq. (3)).[6]



(3)

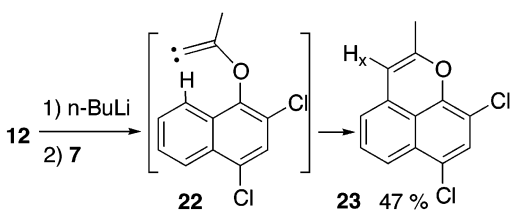
This unsurprising result (cf. Kitamura[3b]) served as a reminder that blocking the *ortho* position of the naphthol was required to redirect the carbene to another site. Eventual optimization of this transformation led to formation of the naphthofuran product **18** in modest yield following slow addition of 3 equiv. of iodonium salt **7** in DME to a refluxing solution of the anion of **15** (*n*-BuLi) in DME (~0.05 M).

Blocking the *ortho* position of 1-naphthol with a methyl group, **13**, provided the first surprise of this study. Combination of naphthol **13** and iodonium salt **7** under the optimized conditions furnished two new naphthopyran products **20** and **21**, separable by reverse-phase HPLC (Eq. (4)).[6] The yield is again modest, although under these conditions starting naphthol is consumed and no other salient signals are detected in the ^1H NMR spectrum of the crude reaction mixture. The few examples of documented 1,6-C–H alkylidenecarbene insertion all involve aromatic C–H bonds,[4] and so formation of the formal aliphatic 1,6-C–H insertion product **21** was unexpected. The ratio of the two products varied slightly as a function of solvent (e.g. 2:1 in THF; 1.5:1 in CH_3CN, 1:1 in DME), but a strong preference for either isomer was never detected. Thus, when faced with no lower energy options, the carbene **19** will engage the C–H bonds positioned six atoms away. No evidence for naphthyloxyalkyne formation via a 1,2-shift was observed, although the presumed lability of a putative alkynyl ether product interjects a note of caution in this analysis.



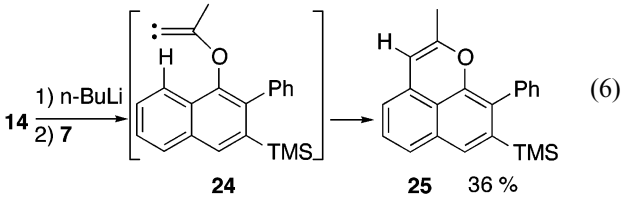
(4)

Once again, substrate modification to eliminate an undesired reaction channel was explored, and the commercially available 2,4-dichloro-1-naphthol (**12**) appeared to be a logical choice in this regard. Condensation of **12** with iodonium salt **7** under the optimized conditions delivered a single product, the formal 1,6-C–H insertion species **23** (Eq. (5)). In this instance, the limited options available to intermediate carbene **22** ensured that only 1,6-chemistry occurred. The insertion product **23** was formed cleanly, and no evidence for other possible products (naphthyloxyalkyne, cycloheptatriene) could be gleaned from spectroscopic examination of the reaction mixture prior to purification. This naphthol substrate performed marginally in CH_3OH (~3% yield), but even that low yield was sufficient to explore the origin of the proton H_x in **23**. Although direct carbene insertion into H_x is plausible, the Gilbert example was shown to proceed through an indirect pathway featuring exchange of H_x with solvent protons.[4a] Combining **12** with **7** in CD_3OD might distinguish between these two divergent pathways. In the event, reaction of **12** with **7** in deuterated methanol delivered a small amount of product **23** with a proton and not a deuterium at H_x (^1H NMR, CIMS measurements, est. ±10%). A control experiment in which **23** was subjected to the standard workup with D_2O instead of H_2O verified that no H/D exchange occurred during this operation. These negative results rule out any mechanism that requires exchange between H_x and solvent.



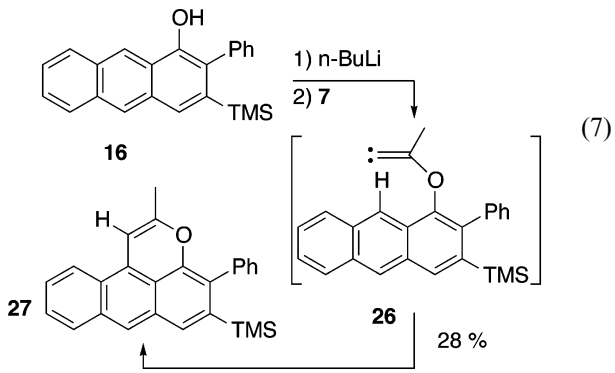
(5)

An additional substrate **14** bearing a blocking *ortho* substituent was examined (Eq. (6)). This species offers another possible site of carbene reactivity by incorporation of a phenyl ring disposed six atoms from the divalent carbon. However, no products which could be ascribed to interaction (addition/rearrangement) of the alkylidenecarbene with the *ipso* position of the pendant phenyl moiety could be identified. Rather, 1,6-C–H insertion at the *peri* site of the naphthol framework once again provided the sole isolated product, **25**.



(6)

A final probe of phenoxy-substituted alkylidenecarbene chemistry was pursued with the anthracene-based substrate **16**. Blocking the phenol's *ortho* position was again expected to direct carbene reactivity to the *peri* position, but in this instance the diminished aromatic resonance energy of the central anthracene ring compared with the analogous ring in the naphthalene series might open the possibility for addition (cf. **10**) rather than insertion chemistry. Reaction of **16** with **7** under the optimized conditions furnished a single isolated adduct, the 1,6-C–H insertion product **27** (Eq. (7)). No evidence for alternative reaction pathways involving carbene addition to either the *peri* site on the anthracene framework or the *ipso* carbon of the phenyl substituent was observed.



(7)

In summary, the alkylidenecarbene generated by addition of 1-naphthol or 1-anthrol addition to an alkynyliodonium salt is quenched by intramolecular C–H insertion. Insertion into an available *ortho* hydrogen is the first option, but blocking this reaction pathway redirects the carbene to an uncommon 1,6-C–H insertion at the *peri* position to furnish pyran-annelated naphthalene or anthracene products. A deuterium incorporation study provides no evidence for the intermediacy of a species bearing solvent exchangeable protons. The products, although formed in modest yield, may find use in the concise assembly of cognate natural products.

Acknowledgements

We thank the National Institutes of Health (GM37681) for financial support of this work.

References

1. (a) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927–10966; (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255.
2. Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164–1170.
3. (a) Kitamura, T.; Zheng, L.; Fukuoka, T.; Fujiwara, Y.; Taniguchi, H.; Sakurai, M.; Tanaka, R. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1511–1515; (b) Kitamura, T.; Tsuda, K.; Fujiwara, Y. *Tetrahedron Lett.* **1998**, *39*, 5375–5376; (c) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K. *J. Org. Chem.* **1995**, *60*, 7722–7723; (d) Shu, T.; Chen, D. -W.; Ochiai, M. *Tetrahedron Lett.* **1996**, *37*, 5539–5542.
4. (a) Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1990**, *31*, 4727–4730; (b) Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J.; McMullen, G. L. *Aust. J. Chem.* **1974**, *27*, 2393–2402.
5. Hartung, Jr., J. B.; Pederson, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 5468–5469
6. Representative experimental: Iodonium salt **7** (590 mg, 1.51 mmol) in 3 mL of CH_3CN was added dropwise to a refluxing solution of the lithium salt of naphthol **13** (from 160 mg (1.01 mmol) and 590 μL of 1.89 M *n*-BuLi (1.12 mmol)) in 7 mL of CH_3CN. After 45 min at reflux, the solution was cooled, subjected to an aqueous workup, and the residue was purified by flash chromatography (hexane on silica gel) to furnish 72 mg (36%) of **20**/**21** as a 1.5:1 mixture. Reverse phase HPLC (C(18), $H_2O/CH_3OH/CH_3CN = 45/10/45$) provided analytical samples of pure compounds. Compound **20**: IR (CH_2Cl_2) 1534.2 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ 7.23 (d, $J = 8.0$ Hz, 1H), 7.09 (m, 3H), 6.48 (d, $J = 6.9$ Hz, 1H), 5.37 (d, $J = 0.9$ Hz, 1H), 2.15 (s, 3H), 1.62 (d, $J = 0.9$ Hz, 3H); ^{13}C NMR (300 MHz, C_6D_6): δ 152.8, 148.2, 133.9, 130.4, 130.3, 127.0, 123.3, 123.2, 119.2, 114.6, 113.9, 96.0, 19.3, 15.2. HRMS calcd for $C_{14}H_{13}O$ (MH^+) 197.0966, found 197.0975. Compound **21**: IR (CH_2Cl_2) 1248.6 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ 8.40 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.35 (m, 3H), 6.87 (d, $J = 8.4$ Hz, 1H), 4.46 (m, 1H), 3.23 (m, 2H), 1.78 (q, $J = 1.7$ Hz, 2H); ^{13}C NMR (300 MHz, C_6D_6): δ 150.6, 147.0, 133.8, 127.9, 127.2, 126.0, 125.9, 124.8, 123.7, 121.7, 115.9, 104.1, 24.9, 19.2; HRMS calcd for $C_{14}H_{13}O$ (MH^+) 197.0966, found 197.0976.