7722 *J. Org. Chem.* **1995**, *60*, 7722–7723

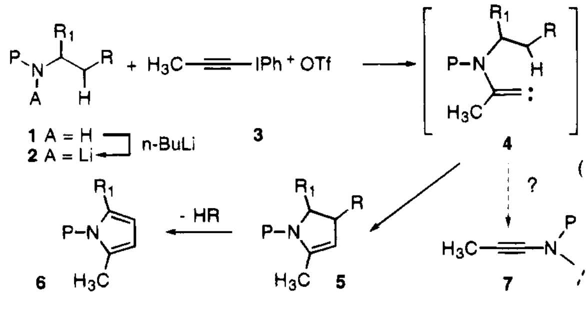
Preparation of Five-Membered Nitrogen-Containing Heterocycles via [Three-Atom + Two-Atom] Combination of Tosylamide Anions with Phenyl(propynyl)iodonium Triflate

Ken S. Feldman,* Michelle M. Bruendl, and Klaas Schildknegt

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

Received September 11, 1995

The combination of select "soft" nucleophiles with alkynyl(phenyl)iodonium salts delivers five-membered ring products in favorable cases provided that at least one component has an appropriately positioned C–H bond.[1–3] This formal [three-atom + two-atom] approach to cyclopentenoid construction capitalizes on the unique dual reactivity (initial nucleophile capture and then vinylidene carbene C–H insertion) intrinsic to the readily available alkyne electrophile. Extensive exploration of the chemistry of alkynyliodonium salts with carbon, oxygen, and sulfur nucleophiles has revealed that the synthetic promise implicit in this bipartite reactivity must be tempered by the observation that reagents falling outside of a rather limited range of nucleophilicity do not participate productively.[1,2] Successful examples of nitrogen-based reagents are at present limited to azide[1c] and Ph_2NLi,[1d] although only the former species leads ultimately to five-membered ring formation. Nevertheless, the prospect of devising a *unified strategy* for the assembly of various five-membered nitrogen-containing heterocycles provides motivation for developing broadly applicable, robust, and effective nitrogen-based nucleophiles which will be useful reaction partners for alkynyliodonium salts. In this paper, we describe the reduction of this strategy to practice for the preparation of dihydropyrrole, pyrrole, and indole products, eqs 1 and 2.

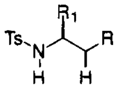


(1)

Table 1. Dihydropyrrole (and Pyrrole) Synthesis from Amides 1 and Iodonium Salt 3

entry		amide substrate 1 P	R	R_1	yield (%)	product dihydropyrrole **5**
a	**1a**	PhCO	Ph	H		**5a**
b	**1b**	F_3CCO	Ph	H	16	**5b**
c	**1c**	F_3CSO_2	Ph	H	28	**5c**
d	**1d**	*p*-tolSO_2	Ph	H	67	**5d**
e	**1e**	*p*-tolSO_2	CH_3	H	72	**5e**
f	**1f**	*p*-tolSO_2	OCH_3	H	53	pyrrole **6f**
g	**1g**	*p*-tolSO_2	$-(CH_2)_4-$		45	*cis*-**5g**

The initial studies were directed toward identifying a protecting group "P" (cf. **1**, R = Ph, R_1 = H) which brings the nitrogen's nucleophilicity within a tolerable range for reaction with the prototype iodonium salt **3**[1f] (Table 1, entries a–d). The *p*-toluenesulfonyl group in **1d** proved superior to the other carbonyl- or sulfonyl-based species examined, and this became the group of choice for subsequent investigations. No evidence for alkyne formation (e.g., **4** → **7**) was obtained in any system examined, in contrast to the ynamine formation observed upon addition of Ph_2NLi to functionalized alkynyliodonium salts.[1d] In general, these transformations are readily effected by slow addition of a slight excess of salt **3** in THF (~0.1M) to a solution of 0.01 M lithium tosylamide **2** (from **1** + *n*-BuLi) at room temperature, followed by aqueous, nonacidic workup. The occasionally acid labile products are isolated following SiO_2 chromatography with a trace of Et_3N in the eluent. A few additional examples (Table 1, entries e–g) demonstrate that both methyl and methoxy substituents at the C–H insertion site are permissible, in accord with the large body of work on vinylidene carbenes that details the indiscriminate nature of these reactive intermediates.[4] The methoxy-substituted dihydropyrrole is too labile to isolate, and facile loss of methanol readily furnishes the corresponding pyrrole **6f**.



1h R = $CH_2OTBDMS$, R_1 = CH_3
1i R = CH_3, R_1 = Ph
1j R = R_1 = Ph

The substrates **1g** and **1h–j** explore (1) the consequence of increased steric hindrance near the nucleophilic site on dihydropyrrole yield and (2) the level of relative asymmetric induction in the alkylidene carbene insertion step. The intermediate **4g** formed upon combination of **1g** with **3** offers diastereotopic hydrogens to the carbenic center. Exclusive insertion into the cis-disposed hydrogen is observed, and only the cis-fused bicyclic product **5g** is formed. The tosylamides **1h–j** also bear a secondary center adjacent to the C–H bond destined to suffer carbene insertion.[5] Only modest amounts (10–25%) of dihydropyrrole products could be detected upon reaction with iodonium salt **3** under a variety of experimental conditions. In each case, unreacted tosylamide was

---

[1] (a) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93. (c) Kitamura, T.; Stang, P. J. *Tetrahedron Lett.* **1988**, *29*, 1887. (d) Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255. (e) Zhdankin, V. V.; Crittell, C. M.; Stang, P. J.; Zefirov, N. S. *Tetrahedron Lett.* **1990**, *31*, 4821. (f) Zhdankin, V. V.; Scheuller, M. C.; Stang, P. J. *Tetrahedron Lett.* **1993**, *34*, 6853. (g) Tykwinski, R. R.; Whiteford, J. A.; Stang, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1800.

[2] (a) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281. (b) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135.

[3] We have recently described the intramolecular bicylization of tosylamide-bearing alkynyliodonium salts to furnish tosyl cyclopentenamide derivatives: Schildknegt, K.; Bohnstedt, A. C.; Feldman, K. S.; Sambandam, A. *J. Am. Chem. Soc.* **1995**, *117*, 7544.

[4] (a) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557. (b) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656. (c) Gilbert, J. C.; Giamalva, D. H. *J. Org. Chem.* **1985**, *50*, 2586. (d) Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1984**, *25*, 4067. (e) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251. (f) Stang, P. J. *Chem. Rev.* **1978**, *78*, 384. (g) Davis, J. H.; Goddard, W. A., III; Harding, L B. *J. Am. Chem. Soc.* **1977**, *99*, 2919. (h) Gallo, M. M.; Hamilton, T. P.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1990**, *112*, 8714. (i) DeLeeuw, B. J.; Fermann, J. T.; Xie, Y.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1993**, *115*, 1039.

[5] Taber has recently described a vinylidene carbene insertion/cyclization that proceeded with 4.4:1 1,2 diastereoselectivity: Taber, D. F.; Meagley, R. P. *Tetrahedron Lett.* **1994**, *35*, 7909.

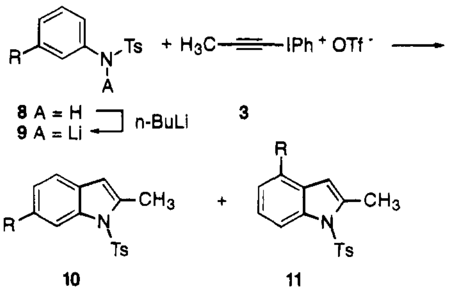
0022-3263/95/1960-7722$09.00/0

Table 2. Indole Synthesis from Anilides 8 and Iodonium Salt 3

entry		toslyanilide **8**, R	yield (%)	indoles **10**:**11**
a	**8a**	H	66	**10a**
b	**8b**	CH_3	59	**10b**/**11b** 1:1
c	**8c**	OCH_3	61	**10c**/**11c** 1.4:1
d	**8d**	CO_2CH_3	51	**10d**/**11d** 1.2:1
e	**8e**	CO_2-*t*-Bu	46	**10e**/**11e** 1.3:1

recovered in good yield. Furthermore, unremarkable diastereoselectivity (typically, 1.2:1) characterized the dihydropyrrole products that were formed from **1h**–**j** . Thus, a substituent adjacent to the nitrogen is scarcely tolerated and is a notable limitation of this chemistry.

Insertion into aliphatic C–H bonds is a property that vinylidene carbenes share with several other reactive electrophilic intermediates. In contrast, they stand almost alone among organic species in their ability to insert into significantly less reactive aryl C–H bonds.[1g] This uncommon attribute can be used to advantage in the synthesis of variously substituted indole rings **10**/**11** from simple tosylanilides **8** and the salt **3**, eq 2 and Table 2. At present, we have no information which addresses the mechanistic details of this transformation (direct C–H insertion as suggested above, or a more complicated and indirect pathway?). Attempts to identify any inherent regioselectivity upon C–H insertion in 3-substituted aryl precursors went largely unrewarded. Thus, only the most modest preference for insertion into the Ar–H bond most distant from the 3-substituent was observed.



(2)

In summary, the tandem nucleophilic addition–vinylidene carbene insertion sequence characteristic of alkynyliodonium salts can be extended to synthesize dihydropyrrole, pyrrole, and indole products by combination with appropriately substituted nitrogen nucleophiles. The minimal functional requirements placed on the nitrogen nucleophile (tosylamide anion, possesses a β C–H bond) suggest that this transformation may underlie a useful strategy for the efficient preparation of structurally complex targets containing these ring systems.

Acknowledgment. We thank NIH GM37681 for financial support.

Supporting Information Available: Full spectral data (^1H NMR, ^{13}C NMR, IR, LRMS, HRMS or elemental analysis) for **5b**–**g**, **6f**, **10a**–**e**, and **11b**–**e** (8 pages).

JO9516594