Communications to the Editor

Rapid Assembly of Substituted Dihydrocyclohepta[3,4]pyrrolo[1,2-*a*]indoles via a Novel, Carbene-Based, Rearrangement Reaction

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Efforts within the Merck Research Laboratories aimed at discovery of new compounds for the treatment of HIV infection have resulted in indinavir (Crixivan, a protease inhibitor) and, most recently, efavirenz (**1**)[1] (Stocrin/Sustiva, a nonnucleoside reverse transcriptase inhibitor). A practical asymmetric synthesis of efavirenz was described recently, based upon asymmetric alkynylation chemistry.[2] To complete the synthesis of **1**, ring closure of the trityl protected propargyl alcohol **2a** (Figure 1) to give **3a**, followed by deprotection, was attempted. Our investigation of this sequence uncovered some remarkable and apparently unprecedented rearrangement chemistry which is the subject of this paper.

Attempted conversion of the *optically active* amino alcohol **2a** into the cyclic carbamate **3a**, using carbonyl dimiidazole (CDI, 25 °C) in several solvents, did not provide **3a**, as expected, but instead resulted in a clean and rapid conversion to the *racemic* dihydrocyclohepta[3,4]pyrrolo[1,2-*a*]indole **4a** (Figure 1). This core heterocyclic structure has not been reported in the literature, and was fully characterized by NMR spectroscopy and by X-ray diffraction analysis.[3] Formation of **4a** apparently proceeds via O-activation with CDI followed by rearrangement featuring ring expansion of one of the phenyl rings of the trityl group.

Further study of this potentially useful rearrangement−ring expansion process focused on the identification of structural features in propargyl alcohols **2** that lead to efficient rearrangement, upon O-activation, to give tetracyclic compounds **4** (Figure 1). In particular, we examined the effect of terminal alkyne substituents (R_1) and the N-protecting group (R_2, R_3, R_4) on the outcome (or rate) of the rearrangement process, to gain some understanding of the reaction mechanism.

For these studies collection of rate data was simplified by O-activation via the acetate; the subsequent rearrangements were much slower than those initiated by CDI, allowing for separation of the activation and rearrangement steps.[4] Thus **2a** was converted cleanly into the corresponding O-acetate, which was rearranged to **4a** simply by heating in solvent.[5] Interestingly, the rearrangement proceeds at a similar rate in a range of solvents[6] and racemic

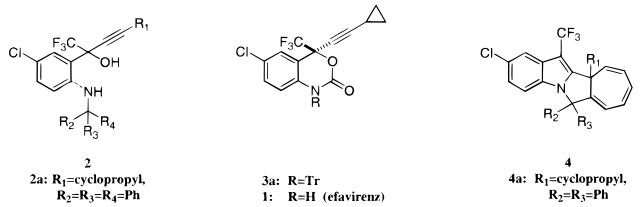

Figure 1. An Unexpected Rearrangement Reaction

Table 1. Rearrangement of the Acetate Esters of Amino Alcohols **2** ($R_2 = R_3 = R_4 = Ph$)

entry	substrate	R_1	product	$t_{1/2}$[a]	yield, %[b]
1	**2a**	cyclopropyl	**4a**	99 min	84
2	**2b**	CO_2Et	**4b**	131 min	80
3	**2c**	H	**4c**	9 h	82
4	**2d**	*n*-Bu	**4d**	115 h	96
5	**2e**	CyHex	**4e**	165 h	40[c]
6	**2f**	Ph	**4f**	101 min	92
7	**2g**	4-NO_2Ph	**4g**	87 min	97
8	**2h**	4-MeOPh	**4h**	67 min	99
9	**2i**	Ph[d]	**4i**	11 min	92

[a] Rearrangement reaction carried out in ACN at 75 °C, using the corresponding acetates. [b] Isolated yield. [c] 35% **2e** remaining. [d] Replacement of CF_3 with Ph.

product arises as a consequence of the rearrangement reaction and *not* from prior racemization of the O-acetate of **2a**.

Rearrangements of several *N*-trityl-protected amino alcohols **2** with different terminal alkyne substituents were studied (Table 1). It is clear that there is a significant terminal alkyne substituent effect on the rate of this reaction, rapid and efficient rearrangement being observed for substrates with terminal substituents capable of conjugation to the triple bond (entries 1, 2, 6−9). Slow rearrangements were observed for substrates with terminal substituents incapable of conjugation to the triple bond (entries 3−5), with larger substituents providing slowest reaction. For phenyl substitution, no significant effects on the rate of rearrangement were observed with electron-donating or -withdrawing groups in the para position (entries 6−8). Replacement of the propargylic trifluoromethyl group in **2f** by phenyl (compare entries 6 and 9) provided an approximate 9-fold increase in reaction rate.

It was considered that placement of an electron-donating (*p*-methoxy) or -withdrawing (*p*-sulfonylmethyl) group in one of the three phenyl rings of the trityl group might influence the product distribution. However, no such electronic effect was observed.[7]

While the rearrangement should, in principle, be possible for any substituted *N*-benzyl propargyl alcohol **2**, it was suspected that the steric environment of the N-atom might impact the efficiency of the rearrangement process. Thus, activation/rearrangement was carried out using substrates in which the phenyls in the *N*-trityl group of **2a** were sequentially replaced by H atoms (Table 2, Scheme 1). Rearrangement of **2j** (*N*-diphenylmethyl protected) proceeded cleanly in 1 h at 75 °C to give the expected tetracyclic product as a 5:1 mixture of diastereomers **4j-a/4j-b** (44%) along with 27% of *tricyclic* compound **5j**, which clearly arises via cyclopropane ring opening.[8] Interestingly rearrangement of **2k** (benzyl protected) proceeded at 75 °C (2 h) to give *only* the tricyclic compound **5k** (Table 2, Scheme 1).

Next, replacement of phenyl groups in **2a** with methyl groups was examined. Surprisingly, rearrangement of **2l** (*N*-dimethylphen-

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(3) (a) This rearrangement was independently observed by Dr. Lilian Radesca, DuPont Pharmaceuticals (personal communication). (b) See Supporting Information for NMR and X-ray data (Figure 1).

(4) Rearrangement is significantly faster for the trifluoroacetyl derivative than for the acetate, implying that C−O bond fission occurs in the rate-determining step.[9]

(5) No difference in rate is observed in the presence of base (triethylamine or imidazole), or using acetate prepared in situ.

(6) First-order kinetics: in ACN, $t_{1/2} = 99$ min, in DMAC, $t_{1/2} = 172$ min; in EtOAc, $t_{1/2} = 209$ min; and in toluene, $t_{1/2} = 267$ min, all at 75 °C.

(7) See Supporting Information.

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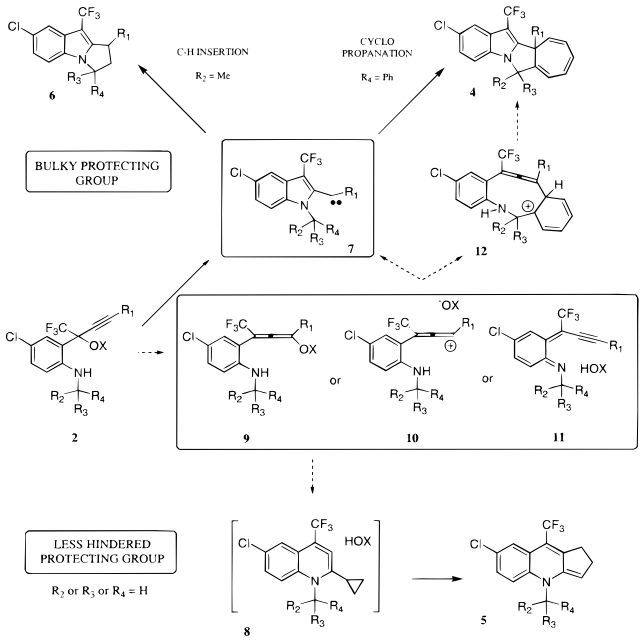
Table 2. Structural Variation in the Protecting Group[a]

	substrate			product **4** (yield)[b]	product **5** (yield)[b]	product **6** (yield)[b]
	R_2	R_3	R_4			
2a	Ph	Ph	Ph	**4a** (84%)		
2j	H	Ph	Ph	**4j-a/4j-b** (44%)	**5j** (27%)	
2k	H	H	Ph		**5k** (51%)[c]	
2l	Me	Me	Ph	**4l** (14%)		**6l-a/6l-b** (71%)
2m	Me	Me	Me			**6m** (93%)

[a] Reactions carried out using the corresponding acetates. [b] Isolated yield. [c] Reaction carried out using the corresponding pivalate, 33% **2k** remaining.

Scheme 1. Possible Reaction Pathways



ylmethyl protected) provided tetracycle **4l** only as the minor product (Table 2). The major product of this reaction was characterized as a 1:1 diastereomeric mixture of tricycles **6l-a/6l-b** which clearly arise via a C−H insertion process! Subsequently, it was found that rearrangement of the *tert*-butyl substrate **2m** provided *exclusively* the C−H insertion product **6m** (Table 2).

The formation of compounds **6l** and **6m** in these reactions has vastly influenced our thinking regarding possible mechanisms for these rearrangement processes (Scheme 1). For substrates with bulky N-protecting groups (**2a**, **2l**, **2m**) it is proposed that O-activation results in slow C−O bond fission[9] with ring closure to give a ***carbene*** intermediate **7**.[10] The carbene **7** undergoes cyclopropanation[11] followed by ring expansion to give the tetracyclic product **4** (from **2a**), or C−H insertion[12] to give the product **6** (from **2m**). Both modes of reaction operate when the protecting group contains both methyl and phenyl groups (e.g. **2l**). In the case of a nonhindered protecting group (e.g. **2k**), it is proposed that O-activation results in cyclization to give the highly strained allene **8**,[13] which undergoes vinylcyclopropane rearrangement, to give exclusively **5**. In the case of a moderately hindered protecting group (e.g., **2k**), it appears that both mechanisms are operating, to give both tetracyclic and tricyclic products. The mechanism for formation of the carbene **7** from the activated propargyl alcohol **2** is not certain. Both direct conversion of the *O*-acetate (or the allenyl isomer **9**) to carbene **7** and pathways involving the stabilized carbocation **10** or the *o*-quinodimethide **11**[14] have been considered. Involvement of carbocation **10** in the rate-limiting step is unlikely on the basis of no solvent effect on the reaction rate, and the observed terminal acetylene substituent effects; similarly, a noncarbene pathway involving rate limiting formation of the cyclic carbocation **12**[15] has also been ruled out on the basis of no observed electronic effect for substituents in the trityl group. Although attempts to trap an *o*-quinoiminomethide intermediate **11**[16] were not successful and no evidence was obtained for formation of the allenyl acetate **9**, reaction via these intermediates cannot be ruled out. Finally, the rate-limiting formation of the carbene **7** followed by rapid collapse to products could be consistent with all observed substituent electronic effects.

In conclusion, activation of tertiary propargyl alcohols **2** results in novel and facile rearrangement reactions leading to the rapid and efficient assembly of heterocyclic structures. The product distributions are affected by the nature and size of the N-protecting group. In the cases of bulky protecting groups, the formation of cyclopropanation−ring expansion products **4** or C−H insertion products **6** overwhelmingly supports intermediacy of carbene **7**. For less hindered protecting groups, six-membered ring formation, accompanied by cyclopropane ring opening, is observed. With appropriate choice of substituents, and N-protecting group, it should be possible to extend the scope of these rearrangement processes to the synthesis of novel, structurally diverse, and potentially important nitrogen-containing heterocycles.

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Supporting Information Available: Experimental details for the rearrangement reaction and spectral data for key tetracycles **4a**, **4b**, **4c**, **4f**, **4i**, tricycle **5k**, and C−H insertion product **6m** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Eisch, J. J.; Gadek, F. J. *J. Org. Chem.* **1971**, *36* (22), 3376−3381.

(9) The small primary kinetic isotope effect ($k_H/k_D = 1.7$, NH vs ND) on the rate of the rearrangement of **2a** to **4a** at 75 °C suggests that N−H bond fission is a feature of the rate-determining step.

(10) We thank the referee for pointing out that a similar process has been reported involving formation of a carbene intermediate from a diradical generated under photolysis conditions. Margaretha, Agosta, and co-workers. Kravitz, J. I.; Margaretha, P.; Agosta, W. C. *Tetrahedron Lett.* **1991**, *32*, 31−34. See also: (a) Mukherjee, A. D.; Margaretha, P.; Agosta, W. C. *J. Org. Chem.* **1996**, *61*, 3388−3391. (b) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Org. Chem.* **1994**, *59*, 5393−5396.

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(15) The cation **12** is formally the product of an intramolecular Friedel−Crafts type alkenylation reaction between a phenyl in the trityl group and **10**.

(16) The observed k_H/k_D could be consistent with slow formation of *o*-quinoiminomethide **12**. However, rearrangement of **2a** in dimethylacetylene dicarboxylate as solvent provided the rearrangement product **4a** and no evidence of a Diels−Alder adduct from reaction with the quinoiminomethide.