ORGANIC LETTERS

2006
Vol. 8, No. 20
4493−4496

New Aspects of Catalytic Intramolecular C–H Amination: Unexpected Formation of a Seven-Membered Ring in Nitrogen-Containing Systems

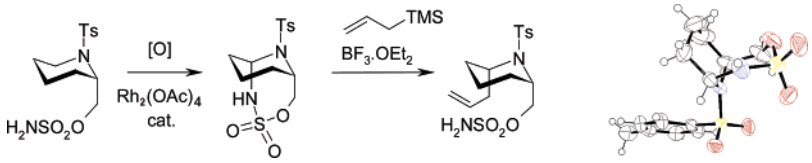
Sylvestre Toumieux,[†] Philippe Compain,*[,†] Olivier R. Martin,[†] and Mohamed Selkti[‡]

ICOA, UMR 6005 CNRS/Université d'Orléans, rue de Chartres, BP 6759, 45067 Orléans, France, and Laboratoire de Cristallographie et RMN Biologiques, UMR 8015 CNRS, Faculté de Pharmacie-Universite Paris V, av. de l'Observatoire, 75006 Paris, France

philippe.compain@univ-orleans.fr

Received July 5, 2006

ABSTRACT



The first example of the formation of a seven-membered ring by way of intramolecular-catalyzed amination of saturated C–H bonds is reported (Du Bois reaction). The influence of various structural parameters was studied, and it was shown that the unexpected regioselectivity observed in nitrogen-containing systems could be rationalized by conformational factors. These results open the way to innovative strategies for the general synthesis of polyfunctionalized piperidines.

Selective transformation of unactivated C−H bonds is a tremendous challenge of wide-reaching consequences in organic chemistry.[1] Major advances have been made very recently in the development of catalytic methods for the amination of unactivated C−H bonds.[2] In 2001, Du Bois and co-workers reported a remarkable, Rh-catalyzed intramolecular C−H insertion process using carbamate or sulfamate ester substrates.[3,4] Amination reactions performed with sulfamate esters led to the formation of the corresponding six-membered ring insertion products, more rarely to five-membered rings, whereas carbamates afforded only five-membered rings (Figure 1). The highly favored formation

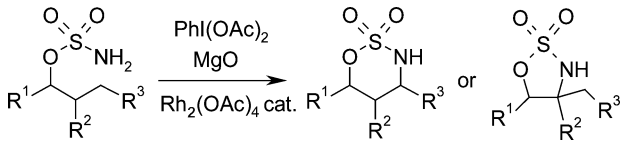


Figure 1. Rh-catalyzed oxidative cyclization of sulfamate esters.

of the oxathiazinane ring may be rationalized by the elongated S−N and S−O bond length and the N−S−O angle of the sulfamate, which match the metrical parameters of the heterocycle.[3a] Additional factors influence the regioselectivity of the reaction. Amination of tertiary C−H bonds

[†] ICOA, UMR 6005 CNRS/Université d'Orléans.
[‡] Laboratoire de Cristallographie et RMN Biologiques.

(1) (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Schreiner, P. R.; Fokin, A. A. *Chem. Rec.* **2004**, *3*, 247. (e) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2004**, 3773. (f) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (g) Dick, A. R. M.; Sanford S. *Tetrahedron* **2006**, *62*, 2439. (h) Davies, H. M. L.; Beckwith, E. J. *Chem. Rev.* **2003**, *103*, 2861. (i) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

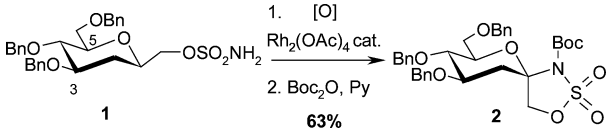
(2) (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571.

10.1021/ol061649x CCC: $33.50
Published on Web 09/07/2006

is generally preferred to secondary C−H bonds, and electron-donating groups activate the α-C−H bond toward insertion.[3c,5]

In connection with our studies on carbohydrate mimics,[6] we recently applied the Du Bois reaction to *C*-glycoside **1** and obtained spiranic oxathiazolidine **2** by regiospecific insertion into the pseudoanomeric C−H bonds (Scheme 1).[5]

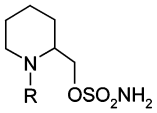
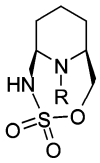
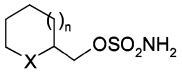
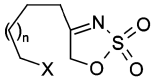
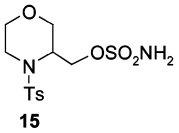
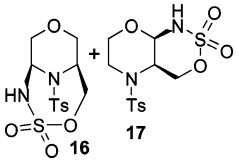
Scheme 1



Quite unexpectedly, this reaction was found to be strongly dependent on the anomeric configuration since no insertion product could be isolated from the pseudo-α-epimer of **1**.

To evaluate the potential of this methodology for the synthesis of original imino-*C*-glycosides, we first performed a model study from piperidine **3**, obtained in two steps from 2-piperidinemethanol (Table 1, entry 1). Amination of the **3** to $PhI(OAc)_2$, MgO, and 5 mol % of $Rh_2(OAc)_4$ in dichloromethane. Surprisingly, no product corresponding to the formation of a six- or five-membered ring was observed. The only insertion product isolated was the oxathiazepane derivative **4** produced in 67% yield (Table 1). Structural evidence for **4**, which corresponds to the insertion product at C-6, was obtained unambiguously by X-ray crystallographic analysis (Figure 2).[7] To the best of our knowledge, **4** is the first seven-membered ring ever obtained by way of Du Bois reaction.[8]

Table 1. Study of the Influence of Various Structural Parameters in Rh-Catalyzed C−H Insertion of Sulfamate Esters[a]

entry	substrate	product	yield[b]
			
1	**3** R = *p*-MePh-SO_2-	**4** R = *p*-MePh-SO_2-	67%
2	**5** R = *p*-OMePh-SO_2-	**6** R = *p*-OMePh-SO_2-	61%
3	**7** R = *p*-CF_3Ph-SO_2-	**8** R = *p*-CF_3Ph-SO_2-	34%
			
4	**9** X = NTs, n = 0	**10** X = NTs, n = 0	29%
5	**11** X = O, n = 0	**12** X = O, n = 0	65%
6	**13** X = O, n = 1	**14** X = O, n = 1	76%[c]
7	 **15**	 **16** **17**	45%

[a] Reaction conditions: CH_2Cl_2, 40 °C, 4−24 h, substrate/$PhI(OAc)_2$/MgO/$Rh_2(OAc)_4$ 1:1.1:2.3:0.05. [b] Isolated yield. [c] Compound **14** was obtained along with 22% of the corresponding spiranic cyclized product.

C-3 position would open the way to a general synthesis of imino-*C*-glycoside analogues of hexosamine whereas nitrogen atom insertion at C-2 would yield a functionalized piperidine containing an aminal structure that could serve as surrogate iminium ions. We thus submitted test substrate

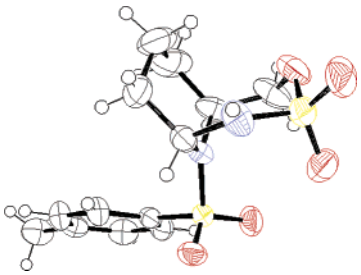


Figure 2. Perspective ORTEP view of compound **4**.

To rationalize this unexpected result, we decided to study the influence of diverse structural parameters (Table 1). Addition of an electron-donating or a strong electron-withdrawing substituent on the phenyl group of the *N*-benzenesulfonylpiperidine decreased the yield but did not change the regioselectivity of the insertion process (entries 2 and 3). Ring size was found to play a key role since no trace amount of an oxathiazepane product could be detected from pyrrolidine **9**. Compound **10** corresponding to the open-chain imine form of the C-2 insertion product was isolated in 29% yield from **9** (entry 4). The nature of the endocyclic heteroatom was also found to be critical. Du Bois reaction performed from pyran and furan derivatives **11** and **13** led

(3) (a) Espino, C. G.; Wehn, P.; Chow, M. J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (c) Fiori, K. W.; Flemming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349.

(4) For examples of related work, see: (a) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728. (b) Fruit, C.; Müller, P. *Helv. Chim. Acta* **2004**, *87*, 1607. (c) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y. Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465. (d) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (e) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (f) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641.

(5) Toumieux, S.; Compain, P.; Martin, O. R. *Tetrahedron Lett.* **2005**, *46*, 4731.

(6) For selected references, see: (a) Godin, G.; Compain, P.; Masson, G.; Martin, O. R. *J. Org. Chem.* **2002**, *67*, 6960. (b) Godin, G.; Compain, P.; Martin, O. R. *Org Lett.* **2003**, *5*, 3269. (c) Compain, P.; Martin, O. R.; Boucheron, C.; Godin, G.; Yu, L.; Ikeda, K.; Asano, N. *ChemBioChem* **2006**, *7*, 1356.

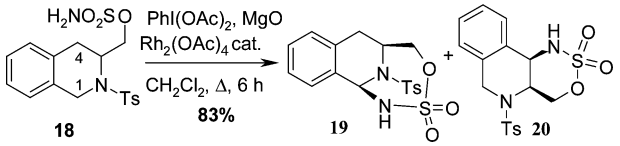
(7) Crystallographic data for structure **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 605300.

(8) For the synthesis of oxathiazepanes by way of PhI═O-mediated copper-catalyzed aziridination of unsaturated sulfamates, see: (a) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H *Org Lett.* **2002**, *4*, 2481. (b) Duran, F. J.; Ghini, A.; Dauban, P.; Dodd, R. H.; Burton, G. *J. Org. Chem.* **2005**, *70*, 8613.

only to products corresponding to the insertion into the C−H bond at C-2 (entries 5 and 6).

The amination reaction was then performed with compound **15**, which was designed to strongly favored the insertion into the ethereal C^{α}−H bonds and thus the formation of the six-membered ring (entry 7). Even in this case, the oxathiazinane derivative **17** was not obtained as the major product as judged by NMR analysis of the crude reaction mixture (ratio **16**/**17** ∼1/1). In another test substrate, the tetrahydroisoquinoline derivative **18** (Scheme 2), the two

Scheme 2

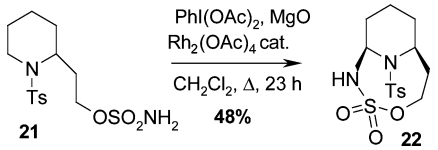


secondary C−H bonds at C-1 and C-4 are benzylic; the amination of the C-4 position may be facilitated by the formation of a six-membered ring whereas insertion into the C−H bond at C-1 may be favored by the presence of an *N*-tosyl group in α.

Under typical amination conditions, the oxathiazepane derivative **19** was obtained as the major product in 65% yield, along with minor amount of the oxathiazinane derivative **20** in 18% yield. The regioselectivity of the reaction was slightly improved by using $Rh_2(esp)_2$, a new C−H amination catalyst (86% yield, ratio **19**/**20** 87/13).[9]

Remarkably, the amination process could be extended to the synthesis of eight-membered rings as it was demonstrated by the reaction performed from sulfamate ester **21**, which was prepared from piperidine-2-ethanol (Scheme 3).

Scheme 3

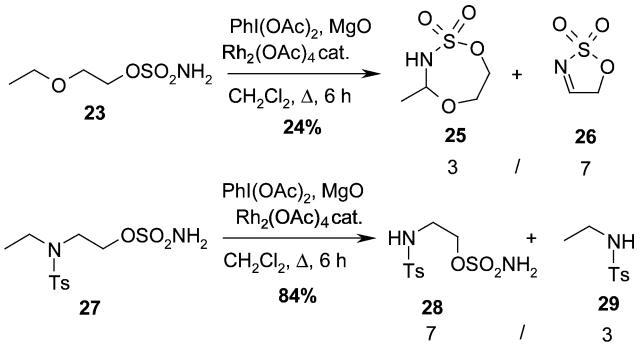


In view of the results obtained, it became clear that the regioselectivity of the amination reaction cannot be attributed solely to electronic factors and that decisive conformational factors were at play. The distinct regioselectivity obtained in the pyran and in the piperidine series may be explained by conformational preferences which placed the nitrene center in a favorable position to the reacting C−H bond.[10] As expected and demonstrated by selective irradiation NMR experiment ($J_{2ax,3ax}$ = 11.1 Hz; $J_{2ax,3eq}$ = 1.7 Hz), pyran **13** adopts a chair conformation with the sulfamoyloxymethyl substituent occupying an equatorial position. This conformation makes the addition into the reactive axial C−H bond[11] at C-2 highly favorable and prevents amination of the C-6 position. In contrast, as supported by X-ray crystallographic analysis (see the Supporting Information) and literature precedent,[12] the piperidine ring of compound **3** may be close in solution to a chair conformation in which the sulfamoyloxymethyl substituent occupies an axial position. Such a conformation minimizes the pseudo $A^{1,3}$ strain between the C-2 substituent and the *N*-tosyl group caused by the partial double bond character of the *S*−*N* sulfonamide bond.[12] This conformation favored the insertion into the reactive axial C−H bond in C-6 to form a seven-membered ring in which the values observed for the S−N and S−O bond lengths (1.59 and 1.56 Å, respectively) and the N−S−O angle (∼106°) are very close to those obtained for oxathiazinane derivatives.[3a] Amination at C-2 is penalized by the formation of a less favored five-membered ring and by the fact that the insertion would occurred in a less reactive equatorial C−H bond.[11]

Puzzling results obtained from *C*-glycoside **1** and its α-epimer make more sense in light of conformational factors (Scheme 1).[5] In **1**, the sulfamoyloxymethyl substituent occupied an equatorial position and thus the oxathiazolidine was readily obtained. In the α-epimer of **1**, this reacting group shifted to an axial position and the insertion could occurred into two activated α-oxygenated axial C−H bonds at C-3 and C-5 leading to the formation of unstable hemiaminal derivatives and thus to degradation.

To reduce conformational control of reaction selectivity, we performed the reaction with acyclic substrates **23** and **27** (Scheme 4). As expected, compounds corresponding to

Scheme 4



the formation of a five- and more importantly a seven-membered rings were observed from amination reaction of

(9) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *125*, 15378.

(10) For conformational control of selectivity in intramolecular carbenoids reactions of diazoacetoacetamides, see, for example: Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q. *J. Org. Chem.* **1991**, *56*, 820.

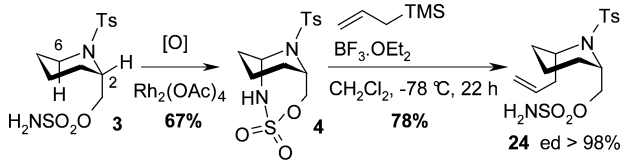
(11) (a) Wardrop, D. J.; Zhang, W.; Fritz, J. *Org. Lett.* **2002**, *4*, 489. (b) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609.

(12) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841. (c) Kuznetsov, N. Y.; Khrustalev, V. N.; Godovikov, I. A.; Bubnov, Y. N. *Eur. J. Org. Chem.* **2006**, 113. (d) Cariou, C. A. M.; Snaith, J. S. *Org. Biomol. Chem.* **2006**, *4*, 51. (e) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7033.

ether **23** (65% of conversion, ratio **25**/**26** 3/7). Because of the relative instability of hemi-aminal derivatives, cyclic sulfonimine **26**, which probably resulted from the corresponding α-ethoxy tosylamide was obtained after purification along with the seven-membered ring **25**. In a similar way, tosylamides **28** and **29** were isolated after treatment of **27** with $Rh_2(OAc)_4$, $PhI(OAc)_2$, and MgO. These compounds most likely came from fragmentation of the corresponding seven- and five-membered ring aminals, respectively.[13]

Beyond its mechanistic interest, the major synthetic significance of the reported process is the substitution of a C−H bond in a 1,7- or 1,8-relationship with respect to the activating group. In addition, the resulting aminals are precursors of *N*-tosyliminium ion: to our knowledge, only one prior report on a related system has shown that such a process is indeed possible.[14,15] A preliminary result obtained with **4** and allylsilane in the presence of $BF_3{\cdot}OEt_2$ nicely demonstrated the feasibility of this approach. The disubstituted piperidine **24** was obtained in good yield and high diastereoselectivity from **4** (Scheme 5).

Scheme 5



X-ray crystallographic analysis (see the Supporting Information) indicated that piperidine **24** adopted a 2,6-cis diaxial conformation since the cis diequatorial conformation would cause strong $A^{1,3}$ strain (Figure 3).[12,16] This step allowed the completely stereocontrolled formation of a C−C bond and also regenerate the sulfamate ester that may be used again for further intramolecular C−H amination of the piperidine ring.

(13) A trace amount of compound **26** was also detected by NMR analysis of the crude reaction mixture.

(14) Berry, C. R.; Hsung, R. P. *Tetrahedron* **2004**, *60*, 7629.

(15) It is noteworthy that aminals **4**, **6**, **8**, **16**, **19**, and **22** are stable for several weeks at room temperature and may be stored for months at 4 °C.

(16) Crystallographic data for structure **24** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 605301.

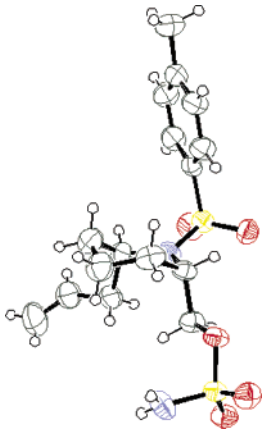


Figure 3. Perspective ORTEP view of compound **24**.

In conclusion, we have reported the first example of the formation of a seven- or eight-membered ring by Du Bois reaction. On the basis of results obtained with various test substrates, it was shown that the unusual regioselectivity observed in nitrogen-containing systems could be rationalized by conformational factors. Our results reveal a completely new aspect of intramolecular C−H amination and further expands its synthetic scope through conformational control of reaction regioselectivity. These findings open the way to unique sequential strategies for the general synthesis of polyfunctionalized piperidines, a major class of biologically active compounds.[17] Further studies along these lines are currently in progress in our laboratory.

Acknowledgment. Financial support by grants from CNRS, the French department of research, and the "Agence Nationale de Recherche sur le Sida" (ANRS) is gratefully acknowledged.

Supporting Information Available: Characterization data for new compounds, experimental procedures, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061649X

(17) See, for example: Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borchedering, D. R. *Tetrahedron* **2003**, *59*, 2953 and references cited therein.