Pergamon

Tetrahedron Letters 39 (1998) 7239–7242

TETRAHEDRON LETTERS

Lewis Acid-mediated Cyclizations of (2'-Amino-*N'-tert*-butoxycarbonyl-benzylidene)-3-alkenylamines

Kristine E. Frank and Jeffrey Aubé*

Department of Medicinal Chemistry
The University of Kansas
Lawrence, Kansas 66045-2506

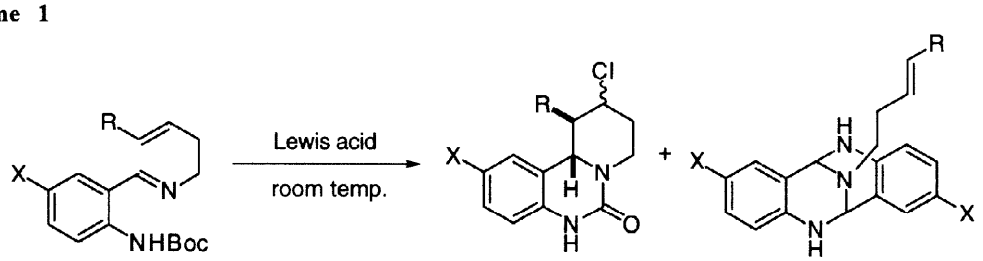
Received 23 June 1998; accepted 21 July 1998

Abstract: Depending on the method of activation, (2'-amino-*N'-tert*-butoxycarbonyl-benzylidene)-3-alkenylamines (**1**) react with Lewis acids ($TiCl_4$ or TMSOTf) to afford either a novel Boc-assisted iminium ion formation/trapping sequence (giving hexahydropyrido[1,2-c]quinazolin-6-ones (**2**) or tetrahydropyrrolo[1,2-c]quinazolin-5-ones (**4**)) or a pseudodimerization process (leading to iminodibenzo[b,f]diazocines (**3**)).

The addition of alkenes to iminium species has been accomplished by a variety of methods. These methods include direct Lewis acid activation of imines,[1,2] the *in situ* preparation of acyl iminium ions from imides,[3] and the formation of iminium ions from reaction of secondary amines with formaldehyde.[4] In the course of our work with (2'-amino-*N'-tert*-butoxycarbonyl-benzylidene)-3-alkenylamines (**1**), we have found that the *N*-Boc substituent assists in the Lewis acid-promoted cyclization of these compounds via an *in situ* acyl iminium species formation. In the absence of the Boc group, a pseudodimerization leading to structures like **3** is de rigeur for this class of compounds.

The syntheses of imines **1a-c** were accomplished by Boc-protection of the aniline,[5] *o*-lithiation/quenching with DMF,[6] and condensation with an alkenyl amine[7] to give the crude imines in 46-61% overall yield. The reaction of **1a-c** with Lewis acids can lead to either hexahydropyrido[1,2-c]quinazolin-6-ones (**2**) or iminodibenzo[b,f][1,5]diazocines (**3**) as shown in Scheme 1.

Scheme 1



1a, X = Cl, R = H
1b, X = Cl, R = Me
1c, X = H, R = H

2a-c **3a-c**

The results of the reactions of **1a-c**, under a variety of Lewis acid conditions, are given in Table 1. The use of TMSOTf led exclusively to the formation of **3** (entries 1 and 6). The yield of this reaction was improved by addition of triethylamine (entry 2). Both **2** and **3** were formed from reaction with $TiCl_4$ (entries 4, 7, and 8). The use of the more mild $TiCl_4/Ti(OiPr)_4$ led to the formation of two diastereomers of **2** (entry 3), but $Ti(OiPr)_4$ by itself was not sufficient to promote either reaction (entry 5).

PII: S0040-4039(98)01596-2

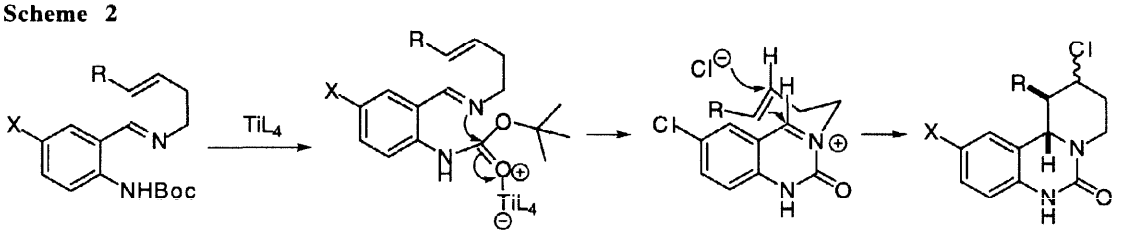
Table 1. Lewis acid-promoted cyclization of imines **1a-c**.

entry	imine	Lewis acid	yield of **2** (%)[a]	yield of **3** (%)
1	**1a**	TMSOTf	*b*	61
2	**1a**	TMSOTf[c]	*b*	81-85
3	**1a**	$TiCl_4/Ti(OiPr)_4$	34 (α) + 13 (β)	*b*
4	**1a**	$TiCl_4$	35-42	ca. 13
5	**1a**	$Ti(OiPr)_4$	*b*	*b*
6	**1b**	TMSOTf	*b*	64
7	**1b**	$TiCl_4$	40	30
8	**1c**	$TiCl_4$	65[d]	*b*

Notes: (a) All products were formed as a >9:1 ratio of α/β chloride epimers except where noted (based on ^1H NMR). (b) Product not isolated. (c) Triethylamine (2.0 equiv) was added. (d) Reaction run in refluxing CH_2Cl_2.

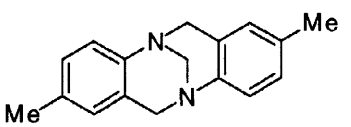
The formation of **2** may be explained by the mechanism shown in Scheme 2. The carbonyl of the Boc group is activated by TiL_4 leading to the formation of an acyl iminium ion. An imine-olefin reaction follows during which chlorine, liberated from the $TiCl_4$, quenches the carbocation. The stereoselectivity of this reaction is rationalized by a chair-like transition state with equatorial attack of chlorine as shown. The intermediacy of the acyl iminium ion has been supported by the observation of lower yields of cyclization products when imines derived from *p*-substituted benzaldehydes and 3-butenylamine are reacted with $TiCl_4$ (even at elevated temperatures)[8] and by the trapping of an acyl iminium ion intermediate with a trichloromethyl group in a related reaction.[9]

Scheme 2



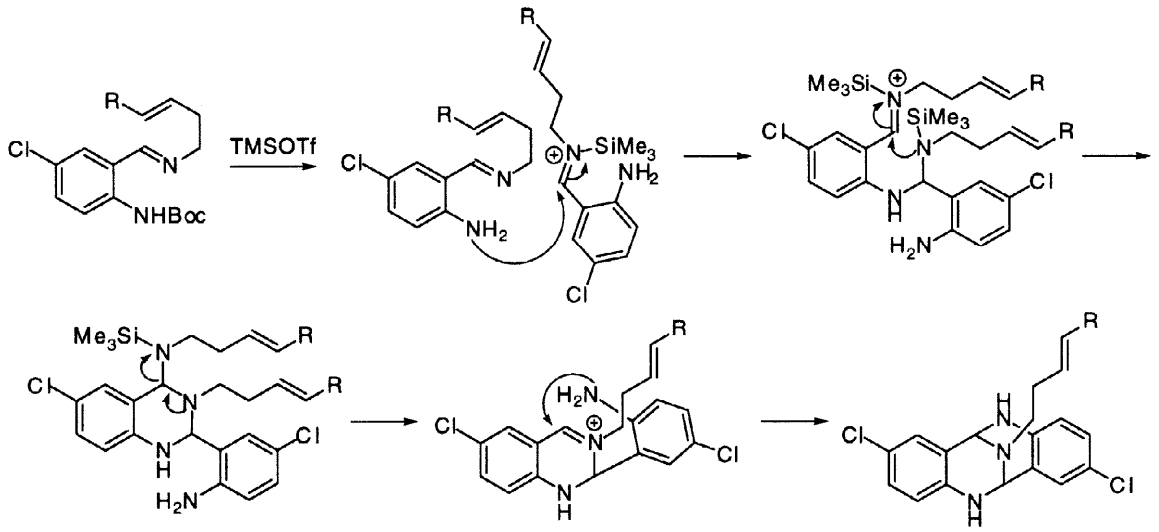
The proposed mechanism for the formation of **3** is shown in Scheme 3. The Boc group is initially deprotected by TMSOTf. The aniline is then free to attack the imine of a second molecule which is most likely TMS-activated. For the sake of simplicity, the second molecule is depicted as already deprotected but it need not be. The resulting amine can then attack the imine of the first molecule in an intramolecular fashion. Once the alkenyl amine is lost, the aniline of the second molecule can add to the resulting iminium ion to give the product.

The formation of systems similar to **3** has been observed in the trimerization of 2-aminobenzaldehyde[10] and in other reactions of *o*-aminobenzaldehydes.[11,12] They have also been prepared from the reaction of the iminophoshorane derived from *o*-azidobenzaldehyde with a variety of primary amines (28-80% yields).[13,14] The interest in these compounds stems from their structural similarity to Tröger's base.



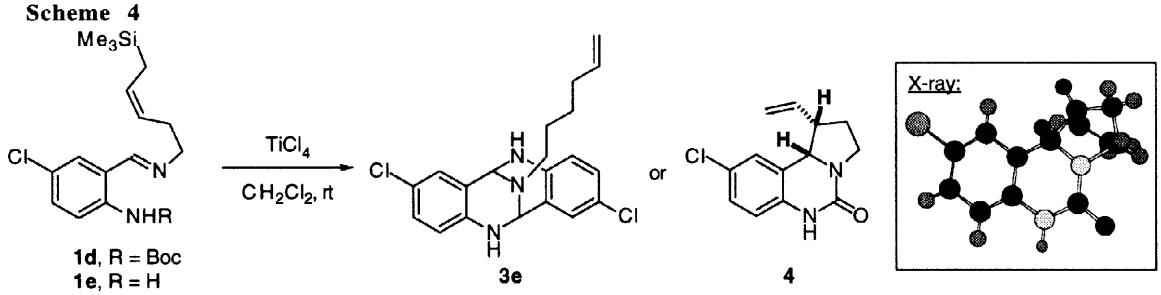
Tröger's base

Scheme 3



The formation of **2** is interesting due to the unique method of imine activation and the incorporation of the chlorine which could undergo substitution, elimination or reduction in a subsequent reaction. It is also important to note that many imine-olefin cyclizations use activated alkenes such as allylic and vinylic silanes and stannanes.[2,15,16] With this in mind, we prepared imines **1d** and **1e** for reaction with $TiCl_4$ (Scheme 4). The preparation of **1d** was accomplished by Boc-protection of *p*-chloroaniline, *o*-lithiation/quenching with DMF, and a one-pot Staudinger/aza-Wittig reaction with (*Z*)-5-azido-1-(trimethylsilyl)-2-pentene (prepared in six steps from 3-butyn-1-ol[15]). Reduction of 5-chloro-2-nitrobenzaldehyde[17] and subsequent Staudinger/aza-Wittig reaction with (*Z*)-5-azido-1-(trimethylsilyl)-2-pentene gave **1e**.

Scheme 4



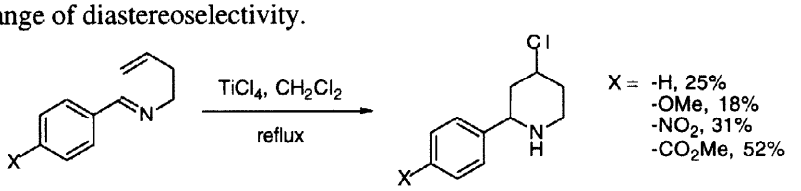
The switchable activation of this series was further explored by examination of imines **1d** and **1e**. The allyl silane was predicted to lead to the formation of a 5-membered ring during the imine-olefin cyclization due to the ability of silyl groups to stabilize β-carbocations.[18] The Boc-containing **1d** gave 9-chloro-1-vinyl-2,3,6,10b-tetrahydro-1*H*-pyrrolo[1,2-c]quinazolin-5-one (**4**) in 62-72% yield with a 95:5 diastereoselectivity for the *cis*-isomer shown (based on ^1H NMR and X-ray). In the absence of the Boc group, **1e** gave only the iminodibenzo[b,f][1,5]diazocine **3e** in 39% yield. This supports the importance of the formation of the acyl iminium species for olefin addition as well as the proposed deprotection of the Boc group by TMSOTf as the initial step in the formation of **3a** and **3b**.

In conclusion, the reaction of (2'-amino-*N'*-*tert*-butoxycarbonyl-benzylidene)-3-alkenylamines (**1**) with either $TiCl_4$ or TMSOTf gives heterocycles which may be useful synthetic intermediates or bases.

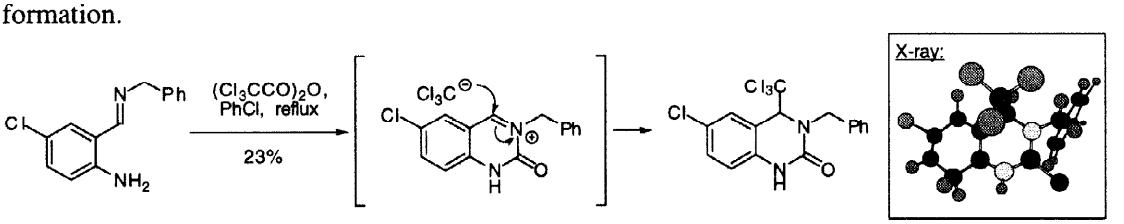
Acknowledgments. This work was supported by the National Institutes of Health (GM 49093). We thank Lawrence Seib for carrying out X-ray crystallographic determinations. K.E.F. also acknowledges receipt of a Madison A. and Lila Self Graduate Fellowship.

References and Notes

1. Demailly, G.; Solladie, G. *J. Org. Chem.* **1981**, *46*, 3102-3108.
2. Park, J.-Y.; Park, C.-H.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 1791-1794.
3. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367-4416.
4. Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352-359.
5. Croce, P. D.; LaRosa, C.; Ritieni, A. *J. Chem. Research (S)* **1988**, 346-347.
6. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798-4801.
7. Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2399-2407.
8. Reaction of (*p*-substituted-benzylidene)-3-butenylamines with $TiCl_4$ gives products in the yields shown with a wide range of diastereoselectivity.



9. Use of trichloroacetic anhydride (1.1 equiv) for activation of the imine shown below leads to cyclic urea formation.



10. Albert, A.; Yamamoto, H. *J. Chem. Soc. (B)* **1966**, 956-963.
11. Black, D. S. C.; Lane, M. J. *Aust. J. Chem.* **1970**, *23*, 2055-2065.
12. Ukhin, L. Y.; Komissarov, V. N.; Litvinov, I. A.; Piven, V. A.; Litvinova, N. A. *Dokl. Akad. Nauk SSSR* **1988**, *303*, 646-651.
13. Molina, P.; Arques, A.; Cartagena, I.; Obón, R. *Tetrahedron Lett.* **1991**, *32*, 2521-2524.
14. Molina, P.; Arques, A.; Tárraga, A.; Obón, M. d. R. *Tetrahedron* **1998**, *54*, 997-1004.
15. Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014-4020.
16. Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107-120.
17. Horner, J. K.; Henry, D. W. *J. Med. Chem.* **1968**, *11*, 946-949.
18. Schinzer, D. *Synthesis* **1988**, 263-273.