ORGANIC LETTERS

2004
Vol. 6, No. 26
4829−4831

2-Aryl-*N*-tosylazetidines as Formal 1,4-Dipoles for [4 + 2] Cycloaddition Reactions with Nitriles: An Easy Access to the Tetrahydropyrimidine Derivatives

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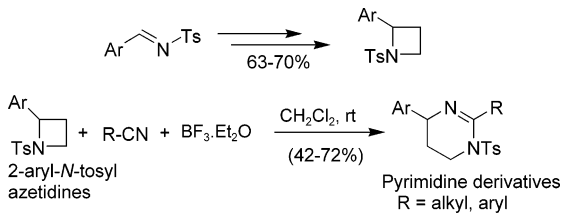
Received September 12, 2004

ABSTRACT



A new synthetic route to 2-aryl-*N*-tosyl azetidines has been developed starting from *N*-tosylarylaldimines in two steps in an overall yield of 63–70%. A formal [4 + 2] cycloaddition of these 2-aryl-*N*-tosylazetidines with nitriles in the presence of $BF_3 \cdot OEt_2$ has been described for the synthesis of substituted tetrahydropyrimidines. It is proposed that the reaction proceeds in Ritter fashion.

Since the discovery of the β-lactam ring as the essential feature of antibiotics, much has been learned about the chemical reactivity of this four-membered heterocycle. The chemistry of 2-azetidinone rings is well-known[1] and used synthetically. However, the chemistry of azetidine has not been much investigated. Many of the efforts involving the azetidine nucleus have been directed toward its synthesis,[2] as it is a component of many biologically active drugs and natural products.[3] Very few examples of rearrangements or fragmentations of the azetidine ring are known. Recently, Mann and co-workers have reported that 2-phenyl-*N*-tosylazetidines, in the presence of a Lewis acid, generate a double exo-stabilized 1,4-dipole or a zwitterion.[4] They have presented evidence for the existence of the 1,4-dipole and utilized it in [4 + 2] cycloaddition reactions with alkenes.[5] Later, the same group extended this formal [4 + 2] cycloaddition to *exo*-methylene cycloalkanes. The formation of spiro-piperidines was precisely anticipated via a formal [4 + 2] cycloaddition reaction.

Although most of the nitriles are known to be poor dipolarophiles for intermolecular [3 + 2] cycloaddition reactions,[6] we recently reported that nitriles are good dipolarophiles for formal [3 + 2] cycloaddition reactions of 2-aryl-

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(2) For reviews on the synthesis and chemistry of azetidines, see: (a) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, 1996; Vol. 1B, Chapter 1.18, pp 507−589. (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds-Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 3, pp 1−217. (c) Cromwell, N. H.; Philips, B. *Chem. Rev.* **1979**, *79*, 331.

(3) (a) Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943. (b) Shuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith, G. F.; Gifford-Moore, D. S. *J. Med. Chem.* **1995**, *38*, 4446. (c) Frigola, J.; R. *J. Med. Chem.* **1994**, *37*, 4195. (d) Dureault, A.; Portal, M,; Carreaux, F.; Depezay, J. C. *Tetrahedron* **1993**, *49*, 4201.

(4) Ungureanu, I.; Koltz, P.; Schoenfelder, A.; Mann, A. *Tetrahedron Lett.* **2000**, *42*, 6087.

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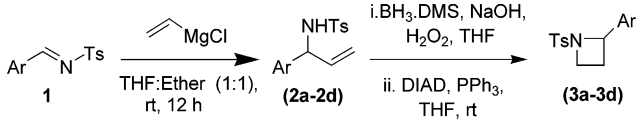
10.1021/ol048161l CCC: $27.50
Published on Web 11/20/2004

N-tosylaziridines for the synthesis of substituted imidazolines in the presence of $BF_3{\cdot}Et_2O$.[7] It is surprising to note that nitriles have not been used as dipolarophiles for synthesis of tetrahydropyrimidines. In this paper, we report the first formal [4 + 2] cycloaddition of 2-aryl-*N*-tosylazetidines with nitriles for synthesis of tetrahydropyrimidines, which are known to exhibit a wide range of pharmacological activities.[8] Further, these tetrahydropyrimidine derivatives are useful synthetic intermediates for synthesis of bacterial siderophores.[9]

Only a few reports are known for synthesis of 2-aryl-*N*-tosylazetidines.[10] However, these methods are not reliable and suffer from poor yields. Hence, there was a need to develop a simple and flexible method for the synthesis of 2-aryl-*N*-tosylazetidines. *N*-tosylarylaldimines **1** were chosen as starting precursors (Scheme 1).[11] The synthesis commences with vinylation of **1** with vinylmagnesium chloride. The resulting addition products (**2a**−**d**) were subjected to hydroboration with $BH_3{\cdot}DMS$ followed by alkaline peroxide treatment. This gave the 1,3-*N*-tosylamino alcohols, which led to the formation of 2-aryl-*N*-tosylazetidines **3** via Mitsunobu reaction in 63−70% overall yield starting from **1** (Table 1).[12]

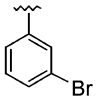
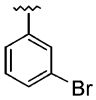
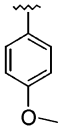
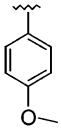
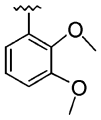
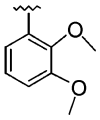
Scheme 1. Synthesis of a Variety of 2-Aryl-*N*-tosylazetidines from *N*-tosylarylaldimines



After successfully demonstrating the synthesis of a variety of azetidines, we studied the reaction of azetidines with nitriles in the presence of various Lewis acids. Among the several Lewis acids examined, $BF_3{\cdot}Et_2O$ was found to be the best for catalyzing the [4 + 2] cycloaddition of 2-phenyl-*N*-tosylazetidine with nitriles. When 20 mol % $BF_3{\cdot}Et_2O$ was used at room temperature, the reaction was completed in 3 h and gave good yields of products. The reaction could be completed in 5 min using 1 equiv of $BF_3{\cdot}Et_2O$, but the yields were very poor. Hence, it was decided to carry out all the reactions with 20 mol % $BF_3{\cdot}Et_2O$, conditions that afforded the products in good yield (Table 2, entries a−e). The other substituted phenyl azetidines gave pyrimidines in moderate yields (Table 3, entries a−f). In the case of 2-(*p*-OMe)-phenyl-*N*-tosylazetidine, the reaction was complete within 15 min at −30 °C even with 20 mol % $BF_3{\cdot}Et_2O$ (Table 3; entries c and d). This could be due to increased stabilization of the benzylic cation by the *p*-OMe group. In most of the cases, the cyclized tetrahydropyrimidines were obtained in moderate to good yield.

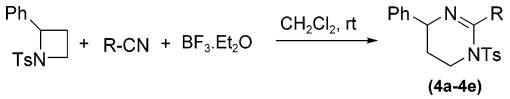
The mechanism of this [4 + 2] cycloaddition reaction is similar to the [3 + 2] cycloaddition of aziridines with nitriles.[7] $BF_3{\cdot}Et_2O$ can attach to the sulfonyl oxygen, and the nitrile group attacks the benzylic center in a typical Ritter fashion, which can lead to the formation of nitrilium salt.

Table 1. Synthesis of (**2a**−**d**) and 2-Aryl-*N*-tosylazetidines (**3a**−**d**) from *N*-tosylarylaldimines **1**

entry	Ar (2a-2d)	yield (%)[a]	Ar (3a-3d)	yield (%)[b]
a	 **(2a)**	92	 **(3a)**	75
b	 **(2b)**	90	 **(3b)**	70
c	 **(2c)**	91	 **(3c)**	71
d	 **(2d)**	94	 **(3d)**	73

[a] Isolated yield for vinyl Grignard addition. [b]Isolated yield after the Mitsunobu reaction.

Table 2. Formal [4 + 2] Cycloaddition of 2-Phenyl-*N*-tosylazetidines with a Variety of Nitriles[a]



(4a-4e)

entry	R	product	time	yield (%)[b]
a	Me	**4a**	2 h	60
b	*i*-Pr	**4b**	3 h	61
c	Ph	**4c**	2 h	72
d	Bn	**4d**	2 h	65
e	CH_2Cl	**4e**	3 h	42

[a] All reactions were performed at room temperature under an argon atmosphere. [b]Isolated yield after column chromatography.

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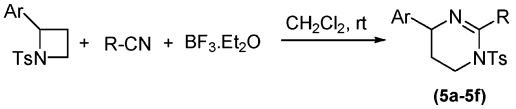
(9) (a) Linger, C.; Azadi, P.; MacLeod, J. K.; Dell, A.; Abdallah, M. A. *Tetrahedron Lett.* **1992**, *33*, 1737 and refs cited therein. (b) Jones, R. C. F.; Crockett, A. K. *Tetrahedron Lett.* **1993**, *34*, 7459.

(10) (a) Gensler, W. J.; Koehler, W. R. *J. Org. Chem.* **1962**, *27*, 2754. (b) Nadir, U.K.; Sharma, R. L.; Koul, V. K. *Tetrahedron* **1989**, *45*, 185.

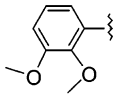
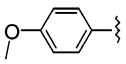
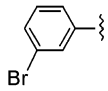
(11) For preparation of aldimines, see: Love, B. E.; Raje, P. S.; Williams, T. C., III. *Synlett* **1994**, 493.

(12) During the hydroboration/alkaline oxidation followed by Mitsunobu reaction, we observed the formation of *N*-tosylaziridines in 15−18% yield, which can be separated by column chromatography in the final step.

Table 3. Formal [4 + 2] Cycloaddition of 2-Aryl-*N*-tosylazetidines with Variety of Nitriles



(5a-5f)

entry	Ar	R	Ar (5a-5f)	time	yield (%)[a]
a		Ph	**5a**	20 min[b]	47
b		Bn	**5b**	20 min[b]	44
c		Me	**5c**	15 min[b]	47
d		Bn	**5d**	15 min[b]	48
e		Ph	**5e**	3 h[c]	49
f		Bn	**5f**	3 h[c]	48

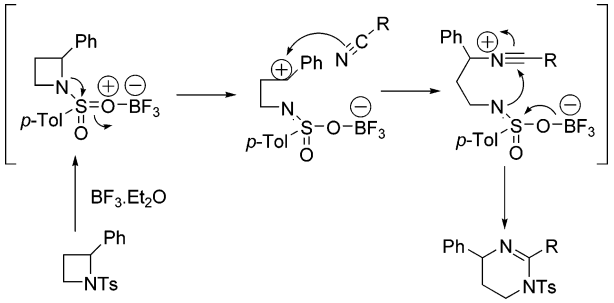
[a] Isolated yield after column chromatography, [b] Performed at −30 °C, [c] Performed at room temperature.

Subsequent attack of the sulfonamide nitrogen led to the formation of tetrahydropyrimidines (Scheme 2).[13]

In summary, we have developed a simple and flexible method for the synthesis of 2-aryl-*N*-tosylazetidines. We have demonstrated for the first time a formal [4 + 2] cycloaddition of 2-aryl-*N*-tosylazetidines with a variety of nitriles and applied this to the synthesis of many substituted tetrahydropyrimidines. We have also shown that most of the nitriles are good dipolarophiles for [4 + 2] cycloaddition reactions with azetidines. These tetrahydropyrimidines will find use in the synthesis of various *N*-substituted compounds after the cleavage of sulfonamide and alkylation.[14,15]

(13) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.

Scheme 2. Proposed Mechanism for Formal [4 + 2] Cycloaddition of 2-Aryl-*N*-tosylazetidines with Nitriles in the Presence of $BF_3{\cdot}OEt_2$



Acknowledgment. We thank Department of Science and Technology, New Delhi, for financial support. A.B. thanks Council of Scientific and Industrial Research, New Delhi, for JRF.

Supporting Information Available: Experimental procedures, compound characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048161L

(14) For cleavage of the *N*-tosyl group, see: (a) Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761. (b) Cantrill, A. A.; Obsorn, H. M. I.; Sweeney, J. *Tetrahedron* **1998**, *54*, 2181. (c) Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511. (d) Vedjes, E.; Sano, H. *Tetrahedron Lett.* **1992**, *33*, 3261.

(15) For cleavage of the *N*-tosyl group by using Mg in methanol, see: Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455. For use of sodium naphthalenide, see: Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181.