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Communications

Stereoselective Synthesis of *trans*-4,5-Disubstituted 1,3-Imidazolidin-2-ones by Reaction of an α-Nitrogen Carbanion with Imines

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The formation and reaction of dipole-stabilized anions adjacent to nitrogen have been studied extensively and are recognized as excellent tools for the synthesis of amine derivatives.[1,2] As shown in Scheme 1, the reaction of α-nitrogen carbanions **1** with imines **2** could be the basis of a useful method for the synthesis of 1,2-diamines **4** if the adducts **3** are formed stereoselectively.[3] 1,2-Diamines and their derivatives are of undisputable importance in organic synthesis. In particular, optically active 1,2-diphenylethylenediamine **4a** (R = Ph)[4] and its derivatives are frequently utilized for enantioselective reactions[6,10] and for optical resolution.[11] We report herein the stereoselective synthesis of *trans*-4,5-disubstituted 1,3-imidazolidin-2-ones **7** by the reaction of the α-nitrogen carbanion of *N*-benzyl-*N*-Boc-*p*-methoxyaniline (**5**) with imines **6** derived from *p*-anisidine (eq 1). This new synthetic route to the cyclic ureas of 1,2-diamines **4** has a distinct advantage in that not only symmetrical **7** (R = Ph) but also unsymmetrical **7** (R ≠ Ph) can be synthesized stereoselectively.[12]

Scheme 1

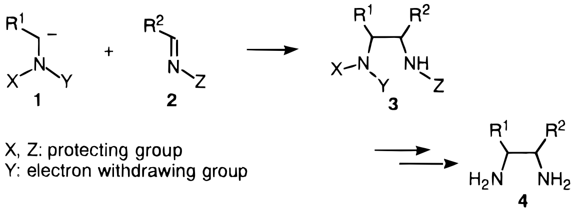
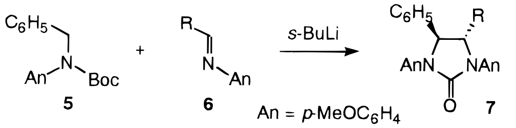


Table 1. Reaction of Lithiated 5 with Imines 6

run	R	imine	solvent	yield (%) of **7**[a]	trans:cis[b]
1	Ph	**6a**	Et_2O	**7a** 87	98:2
2	Ph	**6a**	THF	**7a** 70	93:7
3	*p*-ClC_6H_4	**6b**	Et_2O	**7b** 88	>99:1
4	*o*-MeC_6H_4	**6c**	Et_2O	**7c** 22	>99:1
5	*o*-MeC_6H_4	**6c**	THF	**7c** 92	>99:1
6	*p*-$MeOC_6H_4$	**6d**	Et_2O	**7d** 45	>99:1
7	*p*-$MeOC_6H_4$	**6d**	THF	**7d** 80	84:16
8	*p*-$CF_3C_6H_4$	**6e**	Et_2O	**7e** 88	>99:1
9	2-Furyl	**6f**	Et_2O	**7f** 73	41:59
10	*t*-Butyl	**6g**	Et_2O	**7g** 0	
11[c]	*t*-Butyl	**6g**	Et_2O	**7g** 64[d]	>99:1

[a] Isolated yields. [b] Determined by ^1H NMR. [c] In the presence of $BF_3{\cdot}Et_2O$. [d] Obtained as **8**. See text.



(1)

Deprotonation of *N*-benzyl-*N*-Boc-*p*-methoxyaniline (**5**) was achieved using *s*-BuLi as a base. Treatment of **5** with 1.1 equiv of *s*-BuLi in Et_2O at −78 °C for 2 h followed by the addition of benzylidene-*p*-anisidine (**6a**) as an electrophile (1 equiv) resulted in the formation of 4,5-diphenyl-1,3-imidazolidin-2-one derivative **7a** in good yield (87%) with high trans selectivity (trans:cis = 98:2) (Table 1, run 1). The use of THF as a solvent caused a decrease in both the yield and selectivity (run 2). Imines **6b**−**g** derived from *p*-anisidine also resulted in the corresponding products **7b**−**g** in satisfactory yields as shown in Table 1. In the reactions of (*o*-methylbenzylidene)-*p*-anisidine (**6c**) and (*p*-methoxybenzylidene)-*p*-anisidine (**6d**) (runs 4−7), use of THF as the solvent resulted in better yields than Et_2O, since these imines are sparingly soluble in Et_2O at −78 °C (runs 4 and 6). (2-Furylmethylidene)-*p*-anisidine (**6f**) resulted in the product **7f**, although the diastereoselectivity was low (run 9). *tert*-Amylidene-*p*-anisidine (**7g**) did not react with **5** and was recovered quantitatively under the prescribed conditions (run 10). However, the addition of 1 equiv of $BF_3{\cdot}Et_2O$ to the reaction mixture caused the formation

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(1) For a review, see: Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.

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(3) The reaction of α-nitrogen carbanions formed from *N*-methyl-*N*-benzylphosphoramides with imines was previously reported. The results regarding diastereoselectivity, however, were not described: Savignac, P.; Leroux, Y.; Normant, H. *Tetrahedron* **1975**, *31*, 877.

(4) Optically active **4a** has been obtained by optical resolution of *dl*-**4a** prepared from benzaldehyde[5] or benzil[6] or by transformation from opticall active 1,2-diphenylethane-1,2-diol.[7] Recently, it has been reported that the reductive coupling of imines is an effective method for the stereoselective synthesis of *dl*-**4a**[8] or (*R,R*)-**4a**.[9]

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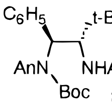
of the adduct **8**, which was converted to **7g** quantitatively by treatment with NaH in refluxing THF (run 11).



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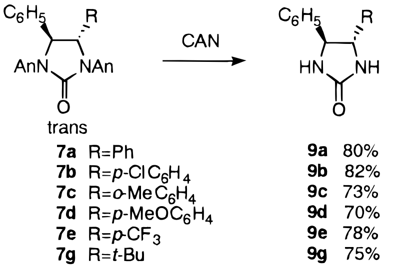
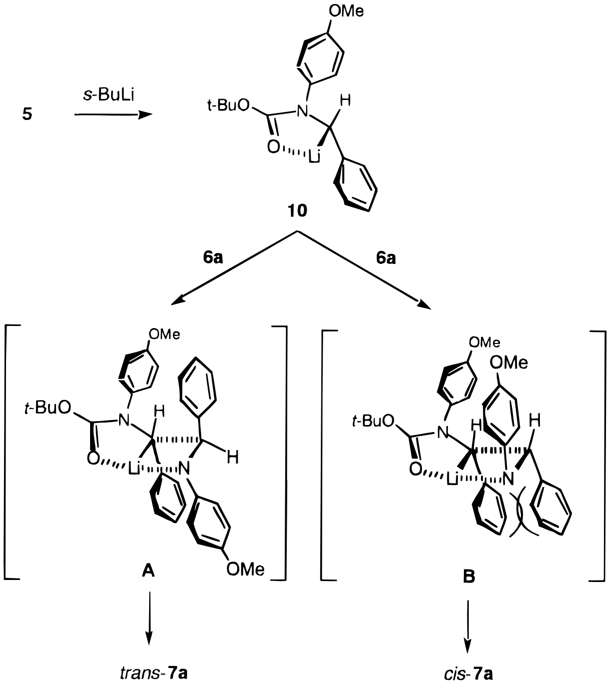
The major isomer of **7a** was deprotected to 4,5-diphenyl-1,3-imidazolidin-2-one (**9a**) in 80% yield upon treatment with ceric ammonium nitrate (CAN) (4.4 equiv) in CH_3CN-H_2O at 0 °C,[13] and the configuration of the obtained **9a** was confirmed to be trans by comparison with an authentic sample.[14] The results of the transformation of ***trans*-7b**−**g** to **9b**−**g** are shown in eq 2.

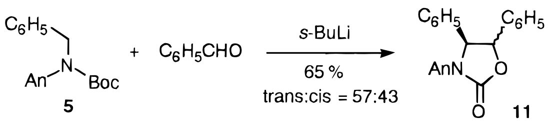


(2)

The high trans selectivity in the formation of **7** can be explained in terms of the transition state shown in Scheme 2. It is reasonable that the lithiated anion of **5** (**10**) is stabilized by the coordination of lithium by the Boc carbonyl oxygen (dipole-stabilized carbanion). If imine **6a** approaches anion **10** with coordination of its nitrogen atom to the lithium metal, transition state **A** is more favorable than **B** due to the lesser repulsion between the two phenyl groups. Therefore, *trans*-adducts are formed predominantly.

Scheme 2





(3)

The reaction of **10** with benzaldehyde resulted in adduct **11** with only modest selectivity (trans:cis = 57:43) (eq 3). Other studies on the reactions of α-nitrogen carbanions with aromatic aldehydes show that the selectivity varies greatly with the structure of the substrate.[15,16] Our results suggest that the use of imines as electrophiles is critical for the high stereoselectivity with carbamate **5**. Further studies to clarify the reaction mechanism and to extend this reaction to the synthesis of other types of 1,2-diamine derivatives are in progress.

Supporting Information Available: Experimental details and compound characterization data (7 pages).

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