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A new synthesis of pyrrolidines via imino-aldol reaction of (2-trimethylsilylmethyl)cyclopropyl ketones with imines

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Abstract

A new synthesis of 2,3,5-trisubstituted pyrrolidines from the imino-aldols formed from Lewis acid-mediated reactions of (2-trimethylsilylmethyl)cyclopropyl ketones with benzylimines is described. The ring closure of the imino-aldols formed from the benzylimines of 2-chloro-, 2-fluoro-, and 2-trifluoromethylbenzaldehydes proceeds with predominantly 2,5-*anti* selectivity to generate the corresponding pyrrolidines in moderate yields.

Keywords: (2-Trimethylsilylmethyl)cyclopropyl ketone; Enolate; Imino-aldol; Hg(II)-promoted aza-ring closure; 2,3,5-Trisubstituted pyrrolidine

The [3+2] addition of aldehydes, ketones, acetylenes, and allenes to 1,3-dipoles generated from silylmethyl-substituted cyclopropanes constitutes a reliable method for the stereoselective synthesis of carbocycles and heterocycles containing an oxygen atom.[1] The enolate generated from the ring-cleavage of a trimethylsilylmethyl-substituted cyclopropyl ketone has previously been reported by us to react with carbonyls to deliver aldol products that were subsequently transformed into tetrahydofuran[2] derivatives under oxidative conditions. As an extension, we considered the reaction of the above enolate with imines to deliver imino-aldols. Reactions allowing the formation of σ_{C-C} bonds from imines have been widely studied due to their important synthetic applications.[3] The above imino-aldol products were transformed further into substituted pyrrolidine derivatives, an important five-membered ring heterocycle due to its frequent occurrence in many biologically active molecules,[4] applications as valuable synthetic intermediates[5] and as organocatalysts.[6] Often the type and degree of substitution about the pyrrolidine ring can have a pronounced effect on the biological activity of a given substrate.

We searched for a protocol for the reaction of cyclopropyl phenyl ketone **1a** with benzylimine of benzaldehyde **2a** mediated by a Lewis acid in dichloromethane. Among the several common Lewis acids, which were examined under different conditions, $TiCl_4$ (1.2 equiv, CH_2Cl_2, 0 °C→rt, 6 h) was found to work reasonably well and the desired products, **3a** and **4a**, were isolated as an 80:20 diastereomeric mixture in 41% combined yield. The **2a**:**1a** stoichiometry was 1.5:1. The remainder of the cyclopropyl substrate was transformed into 3-butenyl phenyl ketone in 46% yield and the imine was hydrolyzed to benzaldehyde and benzylamine. Increasing the **2a**:**1a** stoichiometry to 3:1 did not improve the yield.

The above experiment using suspended K_2CO_3 (2 equiv) furnished the product in a slightly improved 50% yield with an identical diastereomeric ratio (Eq. 1). The remainder of the cyclopropyl substrate was transformed into 3-butenyl phenyl ketone (35% yield). With a view to effectively neutralizing any HCl that may be formed from the hydrolysis of $TiCl_4$ by the adventitious moisture and, thus, prevent quenching of the enolate, an experiment with a combination of $TiCl_4$ and Et_2AlCl (1.2 equiv each, 0 °C→25 °C,

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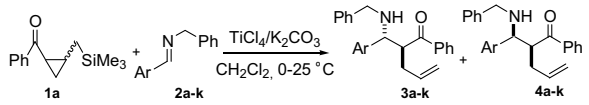
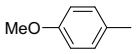
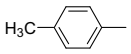
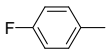
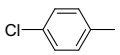
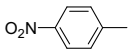
1 h) was carried out.[1e] However, the reaction was complicated and several products were formed. With $BF_3{\cdot}OEt_2$–K_2CO_3 (1.2 equiv $BF_3{\cdot}OEt_2$, 2.0 equiv K_2CO_3, 0 °C→25 °C, 6 h), the diastereomeric ratio was raised to 87:13. However, the yield was poor (24%). The cyclopropane substrate was transformed largely into 3-butenyl phenyl ketone (67% yield). The relative stereochemistry of the imino-aldol products was determined from the relative stereochemistry of the derived pyrrolidine products that, in turn, was determined from NOE experiments (vide infra). We, therefore, used the $TiCl_4$–K_2CO_3 combination and explored other reactions.

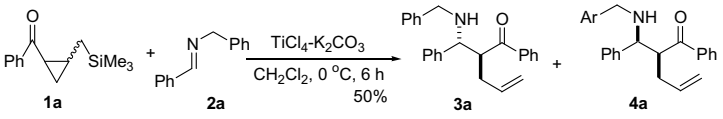
The substituents on the nitrogen of the imine influenced the reaction strongly. *N*-Sulfonylimine was a poor substrate, the reaction was complicated and the desired imino-aldol product was not formed. *N*-*p*-Methoxy-benzylimine afforded the desired imino-aldol products in 41% combined yield as a 77:23 diastereomeric mixture. *N*-Benzylimine, therefore, offered the optimal results in terms of both the yield and the diastereoselectivity.

Having established the feasibility and optimal conditions for the imino-aldol reaction, we studied the reactions of the benzylimines of different aromatic aldehydes with cyclopropane **1a**. The imines were synthesized by condensation of benzylamine and the corresponding aldehydes in 1:1 ratio in dichloromethane in the presence of 4 Å molecular sieves, followed by filtration and concentration. The residue, thus obtained, was used directly for the reactions. As shown in Table 1, the reaction of **1a** with several benzylimines **2a**–**k** furnished the expected imino-aldol products in moderate yields and high diastereoselectivity. The ratio of the two diastereomers ranged from 80:20 to 98:2. Aromatic benzylimines with electron-donating substituents were less reactive than aromatic benzylimines with electron-attracting substituents (cf. entries 2–4 vs 5–11).

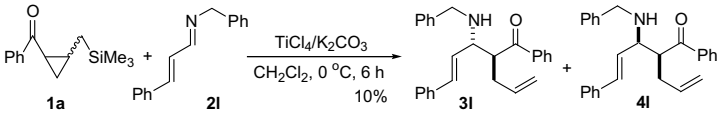
Table 1
Reactions of **1a** with imines **2a**–**k**



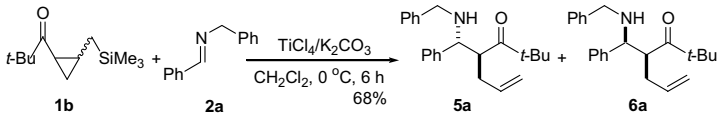
Entry	Ar	Yield of **3** + **4** (%)	dr (*anti*:*syn*)
1		50	80:20
2		30	93:7
3		28	74:26
4		38	88:12
5		43	87:13
6		44	85:15
7		41	80:20
8		47	80:20
9		48	98:2
10		41	80:20
11		43	93:7



(1)



(2)



(3)

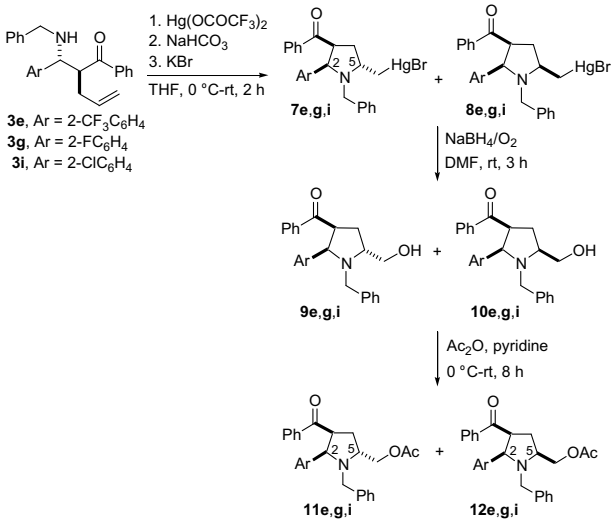
The benzylimines of vinylogous aromatic aldehydes reacted poorly. The reaction of **1a** with the benzylimine of *trans*-cinnamaldehyde **2l** provided the products **3l** and **4l** as an 85:15 diastereomeric mixture in only 10% yield (Eq. 2). The benzylimines of pyridine-3-carboxaldehyde and furfural were hydrolyzed into the corresponding aldehydes and amines and all the cyclopropane had transformed into 3-butenyl phenyl ketone. Likewise, the benzylimine of 3-methyl-2-butenal also did not react; it too was hydrolyzed into its constituents and the cyclopropane substrate had transformed into 3-butenyl phenyl ketone. Aliphatic aldehydes

are, therefore, unsuitable for the present imino-aldol reaction.

We next examined the reaction of *tert*-butyl ketone **1b** with benzylimine **2a** to assess whether the *t*-butyl group had any effect on the observed diastereoselectivity. The reaction of an isomeric mixture of **1b** (*trans*-**1b**:*cis*-**1b** = 1.3:1) with **2a** furnished a 94:6 mixture of the desired imino-aldols **5a** and **6a** in a combined 68% yield (Eq. 3). The species equivalent to 3-butenyl phenyl ketone, that is, 3-butenyl *t*-butyl ketone, was not formed. The higher *anti*-selectivity achieved from *t*-butyl ketone **1b** in comparison to the phenyl ketone **1a** suggests a discerning role of *t*-butyl-vs-phenyl in the transition state during rearrangement.

To demonstrate the synthetic utility of the present imino-aldol protocol, we have cyclized selected imino-aldols into pyrrolidine derivatives following a literature protocol (Scheme 1).[7] Reaction of the imino-aldols, **3e**,**g**,**i**, with $Hg(OCOCF_3)_2$, $NaHCO_3$ and KBr in THF furnished the corresponding diastereomeric organomercurials **7** and **8**. These were subjected to oxidative cleavage of the σ_{C-Hg} bond using $NaBH_4$ and dioxygen to obtain an inseparable mixture of the diastereomeric alcohols **9** and **10**.

The assessment of the diastereomeric ratio was difficult as the key signals in the ^1H NMR spectrum of the mixture of alcohols were not discernible. The task was accomplished by preparing the corresponding acetates **11** and **12**. Further, the relative stereochemistry of the pyrrolidine derivatives was ascertained from rigorous NOE measurements. The two diastereomers shared the same cis-relationship of the substituents at positions 2 and 3 but differed from each other in the stereochemistry of the substituent at position 5. The substituent at position 5 was *anti* to the other two substituents in the major diastereomer **11** and *syn* in the minor diastereomer **12**. The results are collected in Table 2.



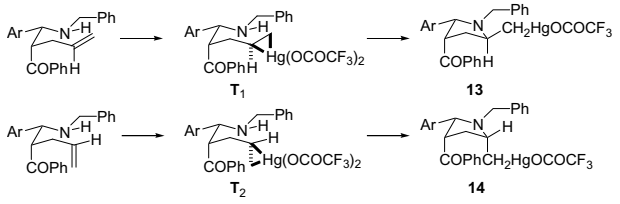
Scheme 1. Oxidative cyclization of the imino-aldols **3e**,**g**,**i** to the corresponding 2,3,5-trisubstituted pyrrolidine derivatives.

Table 2
Conversion of selected imino-aldol products into pyrrolidine derivatives and the diastereomeric ratios

Entry	Ar	Yield[a] (%)	dr (*anti*:*syn*)[b]
1	2-$CF_3C_6H_4$	75	60:40
2	2-FC_6H_4	81	70:30
3	2-ClC_6H_4	72	75:25

[a] Yields given are those of the mixtures of acetates.

[b] The diastereomeric ratio (dr) was determined from the ^1H integrals of the isomeric mixture. The *anti* and *syn* notations refer, respectively, to the relative orientations of the substituents at positions 2 and 5 of the pyrrolidine.



Scheme 2. Possible transition states T_1 and T_2 for the ring closure of **3e**,**g**,**i** to, respectively, the major and minor diastereomers **13** and **14**.

The observed diastereoselectivity from ring closure can be explained by considering the transition state geometries T_1 and T_2 (Scheme 2). Transition state T_2 suffers from 1,3-diaxial steric interactions between the benzoyl group and the methylene group of the mercuronium ion. The preferred transition state T_1, therefore, is responsible for the predominant formation of the 2,5-*anti* isomer through a 5-*exo*-tet ring closure.

In summary, we have developed a method for a highly diastereoselective synthesis of 2,3,5-trisubstituted pyrrolidines via Lewis acid-mediated imino-aldol reactions of aryl (2-trimethylsilylmethyl)cyclopropyl ketones.[8,9] The present methodology allows, for the first time, the Lewis acid-mediated imino-aldol reaction of a cyclopropyl ketone with an imine to generate 5-aminoalkenes, which are amenable to further transformation into 2,3,5-trisubstituted pyrrolidines. An obvious limitation of the present pyrrolidine-forming protocol is the only moderate yield of the imino-aldol product.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.117.

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8. *General procedure for the $TiCl_4$-mediated reaction of* **1a/1b** *with imines*: A freshly prepared solution of $TiCl_4$ (0.60 mmol) in CH_2Cl_2 (0.5 mL) was added to a suspension of **1a/1b** (0.5 mmol) and K_2CO_3 (1 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C. The contents were stirred for 45 min resulting in a red colored solution. A solution of imine (0.75 mmol) in CH_2Cl_2 (0.5 mL) was added, the resultant was stirred for 5 h at 0 °C→rt and then quenched with saturated aqueous $NaHCO_3$ (2 mL) solution. CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extract was washed with water (2 × 7 mL) and brine (1 × 7 mL), and dried. Removal of the solvents furnished the crude product which was filtered through a small column of silica gel using EtOAc/hexane mixtures as eluent. Separation of the diastereomers was achieved by radial chromatography.
9. *A typical procedure for the conversion of an imino-aldol product into the 2,3,5-trisubstituted pyrrolidine derivative*: $Hg(OCOCF_3)_2$ (141 mg, 0.33 mmol) was added to a solution of **3e** (85 mg, 0.22 mmol) in THF (2 mL) and the reaction was stirred for 1 h at rt. Saturated $NaHCO_3$ (1 mL) was added to the reaction mixture under ice cooling. After 30 min of stirring, saturated aqueous KBr (158 mg, 1.32 mmol) was added to the mixture. After 2 h of stirring, the THF layer was separated and the aqueous layer was extracted with EtOAc (3 × 7 mL). The combined organic extract was washed with brine (1 × 7 mL), and dried. After evaporation, the resulting residue was filtered through a small silica gel column to yield the organomercurial bromides **7e/8e**. Oxygen gas was bubbled into a suspension of $NaBH_4$ (13 mg, 0.33 mmol) in DMF (8 mL) for 1 h and the resultant was mixed with a solution of the above organomercurial bromide in DMF (2 mL) with continuous bubbling of oxygen. The bubbling of oxygen was continued for 1 h before ether (10 mL) was added. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was chromatographed on silica gel to yield a mixture of hydroxymethyl derivatives **9e/10e**. This mixture was dissolved in pyridine (0.5 mL) at 0 °C and mixed with Ac_2O (1 mL). The reaction mixture was stirred for 8 h at 0 °C→rt, mixed with EtOAc (10 mL), and washed with water (3 × 10 mL). The organic extract was dried and the solvent was evaporated. The crude product was purified by column chromatography to furnish an 87:13 mixture of **11e** and **12e** as an oil (44 mg, 71%). The acetates were separated by radial chromatography.