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One-Pot Synthesis of Functionalized Piperid-4-ones: A Four-Component Condensation

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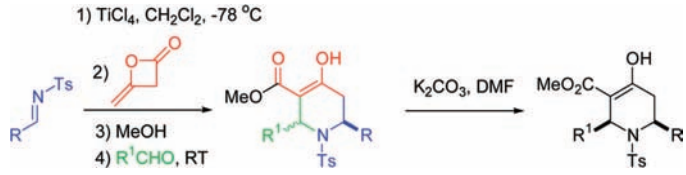
ABSTRACT



The one-pot synthesis of highly substituted piperid-4-ones has been achieved. Diketene is added to a tosyl imine in the presence of $TiCl_4$ and MeOH, followed by 1 equiv of aldehyde to generate 2,6-disubstituted nonsymmetrical piperid-4-ones as a mixture of *cis*-/*trans*-diastereomers in good yields. This mixture of diastereomers can be converted to a single 2,6-*cis*-diastereomer by epimerization with K_2CO_3.

Functionalized piperidines and their derivatives are important pharmacophores which are present in many pharmaceuticals and many molecules in clinical and preclinical trials.[1] Piperidines also occur with great regularity in the natural product arena, and many of these natural products possess promising pharmaceutical potential. Consequently, a huge amount of effort has been directed at their construction by synthetic chemists the world over.[2] Some recent strategies for their synthesis include aza-Prins cyclizations,[3] hetero-Diels−Alder reactions,[4] intramolecular Michael reactions,[5] and cyclization onto iminium ions.[6]

We have become interested in the development of "greener" methods for the synthesis of molecules of medium complexity, especially molecule types which are of interest to the pharmaceutical industry, and we have recently reported the pot, atom, and step economic (PASE) synthesis of highly functionalized tetrahydropyran-4-ones.[7] However, during our discussions with process chemists, we became aware of a need to extend this strategy to the synthesis of functionalized piperidines.[8]

In order to achieve a pot, atom, and step economic synthesis of piperid-4-ones, we re-examined the strategy which we had employed successfully for the synthesis of tetrahydropyran-4-ones,[7] namely the use of diketene as a

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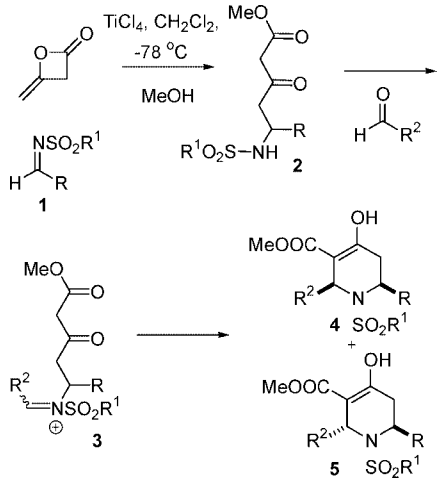
nucleophile,[9] but this time using an imine as the initial electrophile (Scheme 1). We opted to use imines derived

Scheme 1. One-Pot Synthesis of Functionalized Piperidines



from tosyl amide due to their stability toward Lewis acids. Subsequently, we belived that the tosyl group would increase the electrophilicity of the imine and stabilize the Mannich product **2** with respect to a retro-Mannich reaction.

It is possible that the addition of the aldehyde and cyclization to the piperid-4-one may go via one of two possible pathways, either Knoevenagel condensation followed by Michael addition or formation of an iminium **3** followed by "Mannich-like" attack of the enol form of the β-keto ester (Scheme 1);[6] at present, we do not have any evidence to suggest which of these mechanisms is in operation.

A variety of tosyl imines were synthesized from both aliphatic and aromatic aldehydes and treated with diketene in the presence of $TiCl_4$. It was found that the optimum conditions involved premixing the imine with $TiCl_4$ in CH_2Cl_2 at −78 °C, followed by the addition of diketene and then methanol. After 1 h, a solution of the partner aldehyde was added and the reaction was allowed to warm to room temperature. This provided a mixture of diastereomeric piperid-4-ones **4** and **5** in good yields (Table 1).

As can be seen from Table 1, this procedure generated the piperid-4-ones in moderate to excellent yield as mixtures of diastereomers **4** and **5**. Both aryl and alkyl imines and aldehydes could be used, and the tosyl imine could be replaced with a (2-thiophene)sulfonyl imine without adverse effect. The ratio of the diastereomeric piperid-4-ones could be determined by integration of signals in the ^{1}H NMR spectrum; however, at this point, it was not possible to determine which of the diastereomers was the *cis*- or *trans*-isomer. The mixture of diastereomers **4d**−**j** and **5d**−**j** proved inseparable by crystallization or chromatography. Piperid-4-ones **4a**−**c** and **5a**−**c** were separable, but only by laborious

Table 1. Piperid-4-ones Synthesized

entry	imine R =, R^1=	aldehyde R^2=	ratio[a] **4**:**5**	yield (%)
a	Ph, Tol	Ph	5:1[b]	98
b	Ph, Tol	Pr	1.7:1	48
c	Ph, Tol	Me	1:1	72
d	Ph, Tol	*p*-$MeOC_4H_6$	5.3:1	56
e	Me, Tol	Ph	5:1	94
f	Pr, Tol	Me	11:1	88
g	Pr, Tol	Ph	11:1	86
h	Pr, Tol	CH_2OBn	1:1	84
i	iPr, Tol	Me	11.7:1	90
j	Ph, 2-thiophene	Me	1:1	62

[a] Ratio of diastereomers as determined by integration in the ^{1}H NMR signals. At this point, the identity of the major diasteromer could not be determined. [b] The ratio of **4a**:**5a** was 5:1; the identity of the major diastereomer was elucidated by single-crystal X-ray analysis (Figure 1).

preparative thin-layer chromatography. However, even with pure samples of both isomers we were unable to determine by ^{1}H NMR which was the 2,6-*cis*-isomer and which was the 2,6-*trans*-isomer. In our work on tetrahydropyran-4-ones, we were able to determine which isomer was the 2,6-*cis*-isomer by NOE enhancements between the axial H2 and H6 on the 2,6-*cis*-isomer; however, in the case of our piperid-4-ones, neither isomer **4a** or **5a** gave NOE enhancements between the H2 and H6. The identity of the diastereomers was finally determined by single-crystal X-ray analysis.[10] This determined that **4a** was the 2,6-*cis*-diastereomer and **5a** was the 2,6-*trans*-diastereomer. With these structures clarified, it was obvious why there were no NOE enhancements between H2 and H6 in **4a**. The *N*-tosyl group had adopted a pseudoaxial position, which in turn forced the two phenyl groups to sit pseudoaxially. It is possible that this conformation of the ring is stabilized by an aromatic π-stacking interaction between the phenyl groups in the 2- and 6-positions. This, in turn, placed H2 and H6 in pseudoequatorial positions, and hence, no NOE was observed. In the case of the 2,6-*trans*-diastereomer **5a**, H2 and H6 are on opposite faces of the piperid-4-one ring and hence would not have an NOE enhancement either (Figure 1). By use of X-ray single-crystal analysis, we were also able to assign the stereochemical identities of **4b**,**c** and **5b**.

We were disappointed that the reaction furnished two diastereomers and frustrated that with the exception of **4a**−**c** and **5a**−**c** we were unable to separate these diastereomers. In the analogous case of our THP work, the reaction was found to be under thermodynamic control and was reversible; hence, the final THP ratio was the equilibrium ratio under those conditions.[11] It therefore proved possible to separate the diastereomers and resubmit the undesired one to the reaction conditions in order to obtain more of the desired diastereomer. To see if the piperid-4-one-forming reaction behaved in the same way, single diastereomers **4a** and **5a** were resubjected to the reaction conditions independently.

(9) Diketene addition to aldehydes was originally reported by Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 161.

(10) See the Supporting Information.

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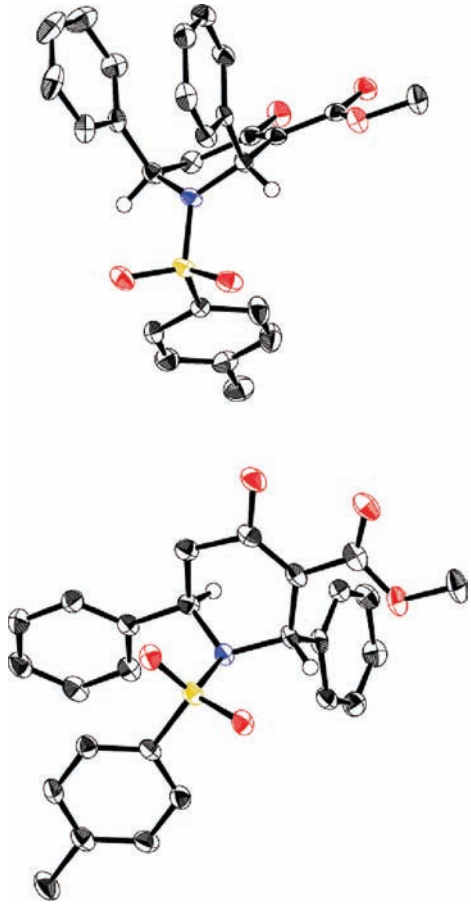
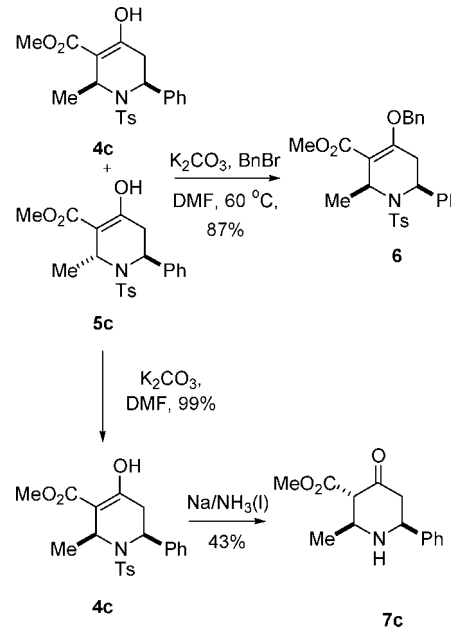


Figure 1. ORTEP diagrams showing the X-ray structures of **4a** (top) and **5a** (bottom). All hydrogen atoms except those at the 2 and 6 positions are omitted. Displacement ellipsoids are drawn at the 50% probability level.

However, even after extended reaction times **4a** and **5a** were reisolated unchanged, implying that the cyclization under these conditions was not reversible.

In an attempt to achieve a separation of the diastereomers **4** and **5**, it was decided to form the enol ether of the mixture of piperid-4-ones and see if these derivatives were easier to separate. To this end, a mixture of piperid-4-ones **4c** and **5c** were treated with K_2CO_3 and benzyl bromide in DMF at 60 °C (Scheme 2). To our dismay, a single new spot by TLC was formed; however, ^{1}H NMR analysis of the crude reaction mixture indicated that a single product had been formed. Analysis of the ^{1}H NMR spectrum showed it to be a single diastereomer of the benzyl enol ether **6**, although it could not be determined, by ^{1}H NMR, whether the 2,6-substituents were *cis* or *trans* to each other. Intrigued by this outcome, a mixture of **4c** and **5c** was subjected to K_2CO_3 in DMF in an attempt to epimerize one of the isomers and form a single diastereomeric piperid-4-one without the need to form the benzyl enol ether. To our delight, a single diastereomer was reisolated which was identical to the diastereomer **4c** which had been assigned as the 2,6-*cis*-diastereomer by single-crystal X-ray analysis.

Scheme 2. Epimerization and Deprotection of Piperid-4-ones **4c**/**5c**



It was decided to remove the *N*-tosyl group in the cases of the other piperid-4-ones in the hope that this would promote a conformational change in the molecule such that ^{1}H NMR and NOE experiments would enable the determination of which diastereomer had been formed rather than rely on single-crystal X-ray analysis. This should reveal the identity of the major diastereomers generated in the other piperid-4-one forming reactions. Removal of the *N*-tosyl group of **4c** was achieved in a 43% yield by the use of Na/liquid NH_3 and provided a single diastereomeric piperid-4-one which was identified as **7c**.

The ^{1}H NMR of **7c** showed that all of the substituents around the ring were equatorial, thus making the 2- and 6-substituents *cis* to each other. We therefore assigned the stereochemistry of the benzyl enol ether **6** as having the 2- and 6-substituents *cis* to each other (Scheme 2). The key data in the assignment of the 2- and 6- substituents of **7c** being *cis* was an NOE of 2.14% between H2 and H6 when H2 was irradiated and an NOE of 2.05% when H6 was irradiated. In addition, H5ax had a vicinal coupling of 12.0 Hz to H6, indicating that the two protons had a *trans*-diaxial relationship to each other, and hence, the methyl and ester groups were *trans* to each other and equatorial.

With this procedure in hand, we subjected the other diastereomeric mixtures of **4a**−**j**/**5a**−**j** to K_2CO_3 in DMF, and in all instances, essentially a single diastereomer resulted[12] which was identical to the major diastereomer formed in the piperid-4-one-generating reaction. With single diastereomers to hand, the *N*-tosyl group was removed with

(12) Traces of the minor diastereomer could just be detected by ^{1}H NMR, and so the ratio after epimerization appears to be greater than 19:1 for **4**:**5**. After removal of the *N*-tosyl group, the minor diastereomer could not be detected.

Na/liquid NH_3 to reveal piperid-4-ones **7b**,**e**−**g**,**i**,**j** in moderate yields (Table 2). It was now possible to assign the major diastereomer in the piperid-4-one-forming reactions as the 2,6-*cis*-diastereomer **4** in every case.

Table 2. Epimerization and Removal of the *N*-Tosyl Group

entry **4/5**	yield of **4** (%)	yield of **7** (%)
a	98	*a*
b	89	60
c	99	43
d	80	*b*
e	91	54
f	93	37
g	80	52
h	83	*a*
I	76	51
j	73	62

[a] Decomposition occurred in the removal of the *N*-tosyl group. [b] Removal of the *N*-tosyl group was not attempted.

As can be seen from Table 2, the epimerization proceeded in good to excellent yields in all cases and the removal of the *N*-tosyl group generated the deprotected piperid-4-ones **7** in moderate to good yields. Attempts to deprotect **4a** and **4h** resulted in decomposition, and no characterizable product was isolated. This is probably due to competing Birch-like reduction of other functionality in the piperid-4-one.

In summary, we have developed an efficient one-pot, atom-economic procedure for the synthesis of 2,6- disubstituted piperid-4-ones from diketene, *N*-tosylimine, and an aldehyde. The procedure is robust in that a variety of coupling partners can be employed giving access to a wide range of substituted piperid-4-ones in high yields.

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Supporting Information Available: Experimental procedures and spectra for all new compounds, and X-ray data for **4a**−**c** and **5a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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