# Synthesis of 1,2,3-Trisubstituted Pyrrolidines and 2,3-Disubstituted Tetrahydrofurans via Diastereoselective Reductive Cyclization of γ-Chloroimines and γ-Chloroketones

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**Abstract:** A new diastereoselective synthetic approach towards 1,2,3-trisubstituted pyrrolidines and 2,3-disubstituted tetrahydrofurans is described. The synthesis of the pyrrolidines involves reductive cyclization of γ-chloroketimines, which were generated in situ from the reaction of 3-substituted 5-chloro-2-pentanones and a primary amine. Various reduction conditions were explored to induce a diastereoselective reductive cyclization. 2,3-Disubstituted tetrahydrofurans were obtained by the direct reduction of 3-substituted 5-chloro-2-pentanones with sodium borohydride.

**Key words:** pyrrolidines, tetrahydrofurans, cyclization, haloimines, haloketones

Substituted pyrrolidines and tetrahydrofurans are common structural subunits found in a broad array of natural and unnatural products with interesting and diverse biological activities.[2] The 1,2,3-trifunctionalized pyrrolidine moiety is present in numerous natural products such as naturally occurring proline analogues.[3] Besides this, 1,2,3-trisubstituted pyrrolidines are useful building blocks for the synthesis of various natural products, as exemplified by the successful synthesis of the natural 1-amidopyrrolizidine alkaloid, (±)-laburnamine, starting from a 1,2,3-trisubstituted pyrrolidine precursor.[4] Furthermore, several 1,2,3-trisubstituted pyrrolidine derivatives exhibit bioactivities such as antitumor, antiosteoarthritis,[5] and antipsychotic activities.[6] On the other hand, the substituted tetrahydrofuran motif is a common core structure of a large family of natural products, namely the annonaceous acetogenins, which possess a range of biological properties such as anthelmintic, antimalarial, antimicrobial, antiprotozoal, cytotoxic, and antitumor activities.[7] In addition, substituted tetrahydrofurans are also found in many other classes of natural products including lignans,[8] polyether ionophores,[9] and macrodiolides.[10] The significant biological interests associated with these compounds has stimulated the scientific community to develop a number of methods for the synthesis of substituted pyrrolidines and tetrahydrofurans. Common ring-formation methods involve radical, electrophilic,[11] and, more recently, palladium-catalyzed cyclizations[2,12] of amino- and hydroxyalkenes,[13] 1,3-dipolar cycloadditions,[14] reductive cyclizations of γ-amino- and γ-hydroxyketones, olefin metathesis reactions, and intramolecular cyclizations by $S_N2$ nucleophilic substitution.[15,16] The latter method mainly involves the stereospecific intramolecular $S_N2$ cyclization of an acyclic substrate in which all stereocenters are already in place.[15,16] In the present paper, an alternative, unexplored synthetic route to 1,2,3-trisubstituted pyrrolidines via diastereoselective reductive $S_N2$ cyclization of γ-chloroketimines and a similar approach for the synthesis of 2,3-disubstituted tetrahydrofurans using γ-chloroketones is disclosed,[17,18] in extension of our research on the application of ω-functionalized imines, and more specifically ω-chloroimines,[19] for the synthesis of heterocyclic compounds.[20] Whereas α-, β-, and δ-haloimines have been used successfully in the reductive cyclization to the corresponding aziridines,[19d–19f] azetidines[19a] and piperidines,[19c,d] respectively, a similar approach towards the five-membered azaheterocycles via reduction of γ-halogenated imines has proven elusive up to now.[19h,20] This important gap in the application of haloimines towards the synthesis of azaheterocycles is partly filled by the results presented herein.

The required starting compounds, that is, 3-alkyl-5-chloro-2-pentanones **1**, were prepared in analogy with alkylation procedures on 2-acetyl-γ-butyrolactone reported in the literature.[21] The imination of γ-chloroketone **1a** with isopropylamine (4 equiv, r.t.) or benzylamine (3.4 equiv, reflux), in the presence of 0.6 equivalents titanium(IV) chloride,[22] resulted in reaction mixtures which were difficult to characterize (Scheme 1). The obtained intermediate imines **2** were not stable enough for characterization by $^1$H NMR or $^{13}$C NMR spectroscopy, and all attempts to isolate them in pure form by distillation failed. The imines **2** tend to cyclize and decompose upon storage even at low temperature. Some analytical and chemical proof for the formation and reactivity of ketimine **2a** was obtained as follows. GC-MS analysis (HP5-MS capillary column) of the reaction mixture containing imine **2a** resulted in thermolysis during analysis with formation of one large peak, together with two minor peaks in a ratio of 98.3:0.8:0.9. The large peak was assigned to pyrroline **3a** (MW = 153), resulting from intramolecular N-alkylation with elimination of HCl. The first eluting minor peak corresponded with the γ-chloroketone **1a** (*m/z* = 148/150). The mass spectrum of the second minor peak showed a signal at *m/z* = 151 and corresponded with the molecular weight of

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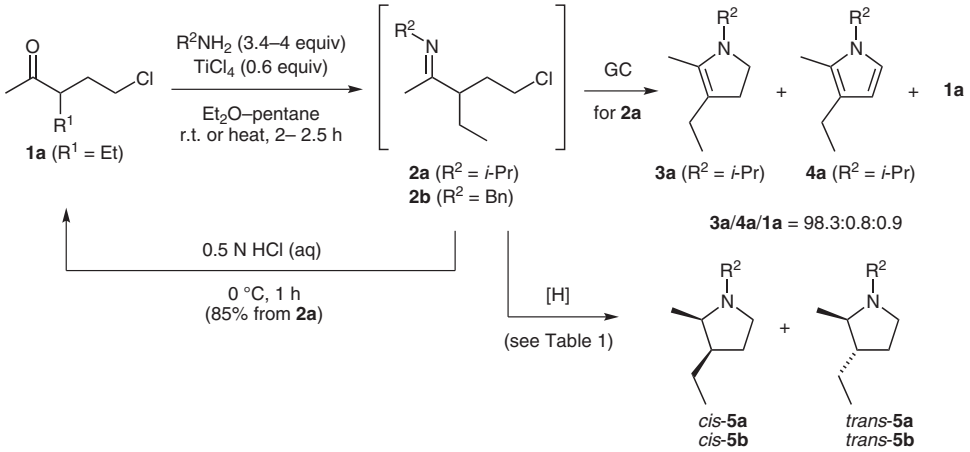



**Scheme 1**

pyrrole **4a**. All attempts to repeat the thermolysis of imine **2a** under more standard conditions by heating in EtOH or DMF under reflux or by microwave heating in DMF or neat resulted in complex reaction mixtures.

The hydrolysis of imine **2a** under mild reaction conditions upon treatment with aqueous 0.5 N HCl at 0 °C for one hour resulted in the regeneration of γ-chloroketone **1a** in 85% yield.

The following reductive cyclizations, with the aim to induce diastereoselectivity during the reduction, were performed on the crude reaction mixtures of imines **2** (Scheme 1, Table 1 and Table S1 in the Supporting Information). Reduction of imine **2a** with two equivalents of sodium borohydride in methanol under reflux resulted in a clean conversion into pyrrolidines *cis*-**5a** and *trans*-**5a**, which were isolated by vacuum distillation as an inseparable 1:1 mixture in 67% overall yield for the two-step process from ketone **1a** (Table 1, entry 1). The *cis*/*trans* ratios and degree of conversion into pyrrolidines **5** were determined by GC. Analogously, reduction of *N*-benzyl imine **2b** with sodium borohydride resulted in the isolation of pyrrolidines *cis*-**5b** and *trans*-**5b** as a 1:1 mixture in 78% overall yield (Table 1, entry 2). The pyrrole **4b** was present as a small impurity in the reaction mixture (ca. 6% determined by GC) and the distillation fraction, and was identified by NMR spectroscopy of an analytical sample obtained via column chromatography on silica gel (Figure 1).

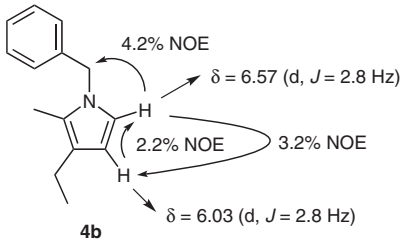



**Figure 1** Structural identification of pyrrole **4b** via $^1$H NMR and DIFNOE experiments

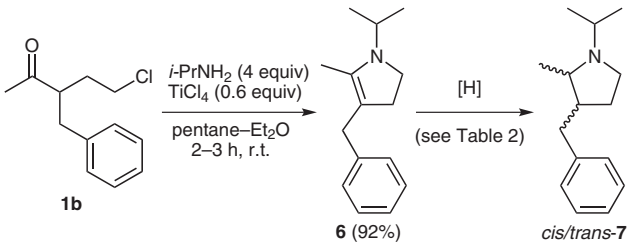
**Table 1** Reductive Cyclization of γ-Chloroketimine **2a** and **2b**

| Entry | Substrate | Reduction conditions | dr *cis*/*trans*[a] | Conv. to **5** (%)[a,b] |
|---|---|---|---|---|
| 1 | **2a** | $NaBH_4$ (2 equiv), MeOH, heat, 2 h | 50:50 | 98 (67) |
| 2 | **2b** | $NaBH_4$ (2 equiv), MeOH, heat, 2 h | 50:50 | 96 (78)[c] |
| 3 | **2a** | $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 2 h | 60:40 | 98 |
| 4 | **2a** | $NaBH_4$ (1.3 equiv), MeOH, –40 °C to –20 °C, 2 h | 52:48 | 92 |
| 5 | **2a** | $NaBH_4$ (1.3 equiv), MeOH, –78 °C to –40 °C, 2 h | 55:45 | 86 |
| 6 | **2a** | $H_2$ (5 atm)/Pd(0) (10 mol%), MeOH, r.t., 3 h | 89:11 | 90 (52) |
| 7 | **2a** | DIBAL (1.3 equiv), THF, –78 °C, 3 h | 77:23 | 64 |
| 8 | **2a** | 9-BBN (1.3 equiv), THF, 0 °C, 3 h | 76:24 | 76 |
| 9 | **2b** | 9-BBN (1.3 equiv), THF, 0 °C, 4 h | 87:13 | 90 (48) |

[a] Determined via GC.
[b] Parentheses indicate overall isolated yields for the two-step process from ketone **1a**.
[c] Contained pyrrole **4b** (< 4% as determined by GC).

All attempts to improve the diastereoselectivity of the reduction of imine **2a** by lowering the reaction temperature during the reaction with sodium borohydride (Table 1, entries 3–5) or by using alternative reducing reagents, that is, $NaBH_4{\cdot}CeCl_3{\cdot}7H_2O$, $NaCNBH_3$, $Zn(BH_4)_2$, $Li(Et)_3BH$, $LiBH_4$, $LiAlH_4$, L-Selectride, and $BH_3{\cdot}SMe_2$, failed, leading to poor diastereomeric ratios (see Supporting Information: Table S1, entries 1–3, 5, 6, 8–10) and/or resulting in lower degrees of conversion into pyrrolidines **5a** (see Supporting Information: Table S1, entries 1, 2, 4, 7, 9–11). However, palladium-catalyzed hydrogenation of γ-chloroketimine **2a** resulted in an improved diastereoselectivity with good conversion affording pyrrolidines *cis*-**5a** and *trans*-**5a** in an 89:11 diastereomeric ratio in an overall yield of 52% (Table 1, entry 6). Alternatively, the use of DIBAL-H or 9-BBN in tetrahydrofuran also afforded good *cis* selectivity with moderate conversion into pyrrolidines **5a** (Table 1, entries 7 and 8). Following the latter method, *N*-benzyl pyrrolidine **5b** as an 87:13 *cis*/*trans* mixture was isolated in 48% yield (Table 1, entry 9). The identification of the *cis*- and *trans*-diastereomers **5a**,**b** was made by NMR analysis of diastereomerically pure samples of *cis*-**5a** and *trans*-**5a** obtained via preparative GC and samples of *cis*-**5b** and *trans*-**5b** obtained via column chromatography on silica gel. In the literature, the *cis*/*trans* configuration of a related 1,2,3-trisubstituted pyrrolidine was assigned based on the $^{13}C$ NMR data of the 2-methyl group.[23] Based on the γ-gauche effect, the *cis* configuration was assigned to the diastereomer with the resonance of the 2-methyl group shifted upfield by 4 ppm ($CDCl_3$) relative to the other diastereomer, that is, the *trans*-pyrrolidine. In analogy, for 3-ethyl-1-isopropyl-2-methylpyrrolidine (**5a**), as well as for 1-benzyl-3-ethyl-2-methylpyrrolidine (**5b**), the resonance of the 2-methyl group of the *cis* diastereomer was shifted upfield relative to the *trans* diastereomer and allowed the assignment of *cis*- and *trans*-**5a**,**b**. The assignment of the *cis* stereochemistry of the *N*-benzylpyrrolidine *cis*-**5b** was further supported by the fact that in this diastereomer C-2 and C-3 were shielded in the $^{13}C$ NMR spectrum when compared with the corresponding resonances of the *trans*-isomer **5b**.[24]

Having found the most stereoselective reduction conditions, that is, palladium-catalyzed hydrogenation at room temperature and the most efficient reaction conditions, that is, reduction with $NaBH_4$ in methanol, the generality of these reductive cyclizations was extended towards the synthesis of 3-benzylated pyrrolidines. Imination of 3-benzyl-5-chloro-2-pentanone (**1b**) with isopropylamine directly afforded, somewhat surprisingly, the corresponding 2-pyrroline **6** in 92% crude yield in >90% purity as determined by GC (Scheme 2). Reduction of the reaction mixture with sodium borohydride or sodium cyanoborohydride in methanol afforded the expected pyrrolidines *cis*- and *trans*-**7** with poor diastereoselectivity (Table 2, entries 1 and 2). The diastereoselectivity could be improved again by palladium-catalyzed hydrogenation leading to the isolation of pyrrolidines **7** as a 78:22 *cis*/*trans* mixture in 42% yield after vacuum distillation (Table 2, entry 3).




**Scheme 2**

With the positive results on the synthesis of 1,2,3-trisubstituted pyrrolidines in hand, the synthesis of valuable 2,3-disubstituted tetrahydrofurans via direct reductive cyclization of γ-chloroketones **1** was investigated. Attempted palladium-catalyzed hydrogenation of γ-chloroketone **1a** failed to give reasonable conversion into the corresponding tetrahydrofurans. When γ-chloroketone **1a** was reduced with sodium borohydride in methanol at 0 °C for three hours no cyclization occurred and the δ-chloroalcohol **8** (dr 67:33) was obtained in 82% yield.

However, when the reduction of ketone **1a** with $NaBH_4$ was performed under reflux conditions in MeOH, the corresponding cyclized 2,3-disubstituted tetrahydrofurans **9** were obtained in 63% yield as a 70:30 *cis*/*trans* mixture in >90% purity (Scheme 3). In analogy with the latter reduction conditions, the 3-benzyl-, 3-methyl-, and 3-allyl-5-chloro-2-pentanones **1b**–**d** were reductively cyclized to diastereomeric mixtures of *cis*- and *trans*-tetrahydrofurans **10**–**12** in good to excellent yields and purity. The synthesized tetrahydrofurans could be further purified via fractionated distillation. 2,3-Dimethyltetrahydrofuran (**11**) has been identified as a significant volatile compo-

**Table 2** Reduction of 2-Pyrroline **6**

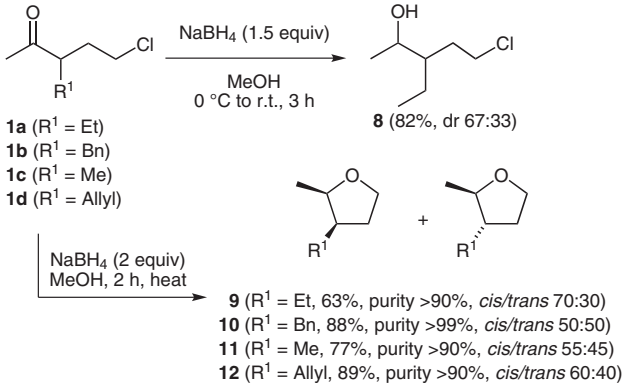
| Entry | Reduction conditions | dr *cis*/*trans*[a] | Conv. to **7** (%)[a,b] |
|---|---|---|---|
| 1 | $NaBH_4$ (2 equiv), MeOH, heat, 2 h | 55:45 | 96 (66) |
| 2 | $NaCNBH_3$ (2 equiv), MeOH AcOH (1 equiv), heat, 2 h | 40:60 | 94 |
| 3 | $H_2$ (5 atm)/Pd(0) (10 mol%), MeOH, r.t., 3 h | 78:22 | 93 (42) |

[a] Determined via GC.
[b] Parentheses indicate overall isolated yields for the two-step process from ketone **1b**.

**Table 3** Reduction of γ-Chloroketone **1c**

| Entry | Reaction conditions | Result |
|---|---|---|
| 1 | $NaBH_4$ (2 equiv), MeOH, 2 h, heat | **11** (77%, purity >90%, *cis*/*trans* = 55:45) |
| 2 | $NaCNBH_3$ (2 equiv)<br>AcOH (1 equiv), MeOH, 2 h, heat | **11** (66%, purity >90%, *cis*/*trans* = 40:60) |
| 3 | $LiAlH_4$ (2 equiv), $Et_2O$, 2 h, heat | **11** (55%, purity >80%, *cis*/*trans* = 70:30) |

nent of the odor spectrum produced by streptomycetes, which are cultivated for the production of important biologically active compounds, for example, antibiotics.[25] The use of alternative reducing reagents had only a moderate influence on the diastereoselectivity of the reductive cyclization of γ-chloroketone **1c** (Table 3), with $NaCNBH_3$ affording a 40:60 *cis*/*trans* mixture of tetrahydrofurans **11** (Table 3, entry 2) and $LiAlH_4$ (Table 3, entry 3) providing a better diastereoselectivity (70:30 *cis*/*trans*) but lower yield and purity.




**Scheme 3**

The assignment of the *cis* and *trans* configuration of the 2,3-disubstituted tetrahydrofurans **9**–**12** was based on comparison of spectroscopic data with literature data for the known 2,3-dimethyltetrahydrofurans (*cis*- and *trans*-**11**),[26] $^1$H NMR NOE experiments, and analysis of $^{13}$C NMR data of the *cis* and *trans* diastereomers **9**–**12**, which could be separated via preparative GC.

It is stated in the literature that the carbon atoms of the ring and the α-carbon atoms of the substituents on C-2 and C-3 in *cis*-tetrahydrofurans are shielded in the $^{13}$C NMR spectrum when compared with the corresponding resonances of the *trans* isomers.[27]

In summary, a novel unexplored diastereoselective synthetic approach towards the synthesis of 1,2,3-trisubstituted pyrrolidines and 2,3-disubstituted tetrahydrofurans is described. The synthesis of the pyrrolidines involves reductive cyclization of in situ prepared γ-chloroketimines or reduction of the 2-pyrroline formed directly by imination of 3-benzyl-5-chloro-2-pentanone. An extensive study was performed to obtain good diastereoselectivity during the synthetic protocol. In terms of yields, sodium borohydride came out as the best reductant, whereas for diastereoselectivity, palladium-catalyzed hydrogenation or, alternatively, reduction with 9-BBN proved to be the best choice. Similarly, 2,3-disubstituted tetrahydrofurans were obtained by the direct reduction of γ-chloroketones.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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