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# Synthesis of New Chiral 6-Carbonyl 2,3,8,8a-Tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines

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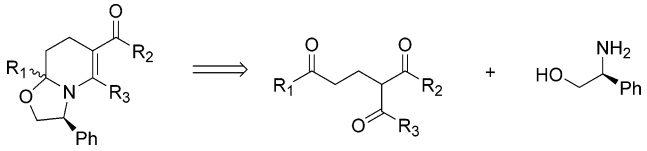


The preparation of new chiral 6-carbonyl 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines by an efficient two-step procedure is described.

In our continuing efforts aimed at the synthesis of chiral polyfunctional heterocycles as precursors of natural products, we recently reported the preparation of bicyclic piperidine $\beta$-enamino esters **1** (Figure 1) by condensation of (*S*)-phenylglycinol with $\omega$-oxo alkynoates and/or $\beta$-keto esters.[1] We and others have demonstrated that such compounds bearing an exocyclic double bond are interesting precursors to access to enantiopure mono- and disubstituted piperidine $\beta$-amino esters that in turn are useful intermediates in the total synthesis of alkaloids.[2] During the course of this work, we realized that our strategy could be extended toward $\beta$-enamino carbonyl derivatives **2** possessing an intracyclic double bond (6-carbonyl 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines) (Figure 1). Indeed, we envisioned that these compounds would give rise to enantiopure 3-hydroxy-2,6-disubstituted piperidines that constitute a large group of natural products such as *Cassia* and *Prosopis* alkaloids.[3] Due to their important biological activity, these compounds have attracted particular attention from many research groups.[4] Herein, we wish to report the results of this program that successfully afforded unsaturated bicyclic piperidines **2**.

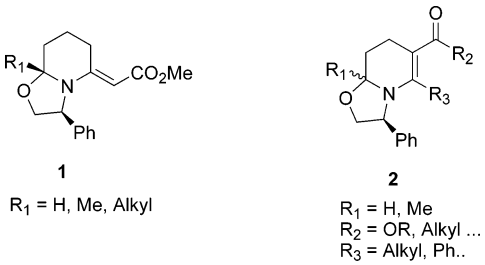
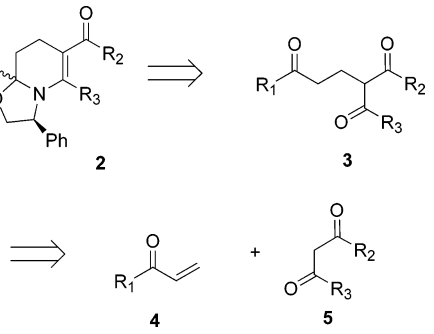



**FIGURE 1.**

**SCHEME 1**




Whereas piperidine $\beta$-enamino carbonyl substructures have been prepared from $\beta$-enamino carbonyl substrates either upon addition of acrylates (to provide unsaturated $\delta$-lactam products[5]) or by intramolecular alkylation,[6] our approach to the target bicyclic molecules **2** relied on the condensation of (*S*)-phenylglycinol to tricarbonyl compounds **3**. The latter compounds were expected to be easily obtained by reaction of active methylene compounds **5** with $\alpha,\beta$-unsaturated carbonyl derivatives **4** (Scheme 1). This approach allows the synthesis of variously substituted structures while sparing the chiral auxiliary since the latter is introduced in the late stages of the synthesis.

To illustrate the potential of this approach, we decided to focus our work on **4a**,**b** ($R_1$ = H or Me). The required tricarbonyl compounds **3** were thus readily prepared by reacting either acroleine **4a** or methylvinyl ketone **4b** with a variety of commercially available substituted $\beta$-dicarbonyl compounds **5** (Table 1). Michael reactions of dicarbonyl compounds **5** with acrolein **4a** were performed on solid $Al_2O_3$ without solvent according to a literature procedure[7] to lead to the expected products in

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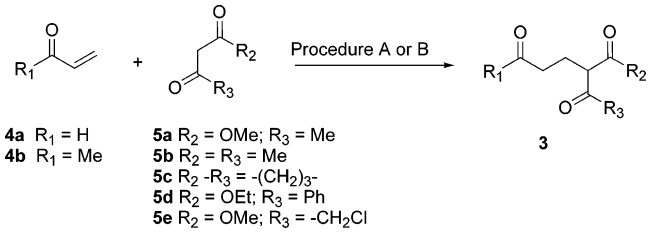
**TABLE 1. Preparation of Tricarbonyl Compounds 3**



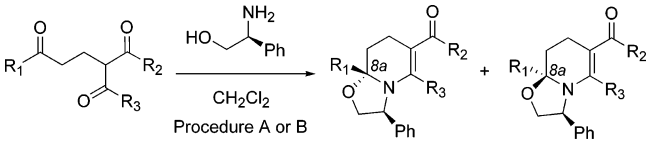

| entry | 4 | 5 | $R_1$ | $R_2$ | $R_3$ | procedure[a] | 3 (yield, %)[e] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | **5a** | H | OMe | Me | A | **3a**[9] (60) |
| 2 | **4b** | **5a** | Me | OMe | Me | B[b] | **3b**[10] (95) |
| 3 | **4a** | **5b** | H | Me | Me | A | **3c**[11] (64) |
| 4 | **4b** | **5b** | Me | Me | Me | B[c] | **3d**[12] (90) |
| 5 | **4a** | **5c** | H | $-(CH_2)_3-$ | | A | **3e** (37) |
| 6 | **4b** | **5c** | Me | $-(CH_2)_3-$ | | B[d] | **3f**[13] (57) |
| 7 | **4a** | **5d** | H | OEt | Ph | A | **3g**[14] (53) |
| 8 | **4b** | **5d** | Me | OEt | Ph | B[b] | **3h**[15] (59) |
| 9 | **4a** | **5e** | H | OMe | $CH_2Cl$ | A | **3i** (80)[f] |
| 10 | **4b** | **5e** | Me | OMe | $CH_2Cl$ | B[b] | **3j** (59) |

[a] Procedure A: $Al_2O_3$, 0 °C, 10 min. Procedure B: $Ni(acac)_2$. [b] Without solvent, 48 h, 40 °C. [c] Dioxane, 19 h, 95°C. [d] Benzene, 40 h, 80°C. [e] Yields refer to isolated compounds after column chromatography. [f] Crude yield. **3i** was used without purification in the next step due to its instability.

moderate yields (Table 1, entries 1, 3, 5, 7, and 9). Regarding the reactions of methylvinyl ketone **4b**, the use of $Ni(acac)_2$ as a catalyst[8] allowed the preparation of the target compounds in good to excellent yields (Table 1, entries 2, 4, 6, 8, and 10).

Compounds **3** were reacted with (*S*)-phenylglycinol generally in $CH_2Cl_2$ according to two procedures (Table 2). In procedure A, we conducted the reaction in the presence of 4 Å molecular sieves between room and reflux temperature. In the particular case of the substrates **3** stemming from methylvinyl ketone ($R_1$ = Me, entries 3, 7, 11, 15, and 19), the presence of catalytic amounts of *p*-TSA was necessary to achieve faster and cleaner reactions. In procedure B, we performed the condensation of (*S*)-phenylglycinol on compounds **3** in the presence of catalytic amount of $Zn(ClO_4)_2 \cdot 6H_2O$ and $MgSO_4$, as recently reported for the condensation of amines with $\beta$-ketoesters.[16] In both cases, we had to optimize reaction conditions in order to improve yields. Initially, we found that conversion rates of expected compounds **2** were drastically improved upon using 2 molar equiv of tricarbonyl compounds **3** for 1 equiv of the amine, rather than using equimolar amounts of reactants. However, in a few cases, the improved conversion rates did not translate into better isolated yields due to our difficulties to separate by column chromatography the excess of substrate **3** from the products **2**. In these cases, better isolated yields were obtained by using **3** and (*S*)-phenylglycinol in a 1:1.1 ratio (Table 2, entries 7−10). Whatever the amount of **3** used in these various reactions, it should be noted that the diastereomeric excesses of compounds **2** were identical.

**TABLE 2. Preparation of Compounds 2**




| entry | 3 | $R_1$ | $R_2$ | $R_3$ | product | procedure[a] | ratio[f] (8a*R*)-**2**/ (8a*S*)-**2** | yield[g] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **3a** | H | OMe | Me | **2a** | **A**[c] | 40:60 | 96 |
| 2 | | | | | | **B** | 25:75 | 81 |
| 3 | **3b** | Me | OMe | Me | **2b** | **A**[b,d] | 85:15 | 87 |
| 4 | | | | | | **B** | 92:8 | 61 |
| 5 | **3c** | H | Me | Me | **2c** | **A**[c] | 30:70 | 86 |
| 6 | | | | | | **B** | 40:60 | 86 |
| 7 | **3d** | Me | Me | Me | **2d** | **A**[b,c] | 92:8 | 64[h] |
| 8 | | | | | | **B** | 92:8 | 26[h] |
| 9 | **3e** | H | $-(CH_2)_3-$ | | **2e** | **A**[c] | 33:67 | 81[h] |
| 10 | | | | | | **B** | 13:87 | 91[h] |
| 11 | **3f** | Me | $-(CH_2)_3-$ | | **2f** | **A**[b,d] | 75:25 | 86 |
| 12 | | | | | | **B** | 90:10 | 90 |
| 13 | **3g** | H | OEt | Ph | **2g** | **A**[d,e] | 34:64 | 60 |
| 14 | | | | | | **B** | 12:88 | 91 |
| 15 | **3h** | Me | OEt | Ph | **6** | **A**[b,d] | | 70 |
| 16 | | | | | | **B** | | 89 |
| 17 | **3i** | H | OMe | $CH_2Cl$ | **2i** | **A**[c] | 45:55 | 76 |
| 18 | | | | | | **B** | 40:60 | 89 |
| 19 | **3j** | Me | OMe | $CH_2Cl$ | | **A**[b,c] | | *i* |
| 20 | | | | | | **B** | | *i* |

[a] Procedure A: 4 Å molecular sieves. Procedure B: $Zn(ClO_4)_2 \cdot 6H_2O$, $MgSO_4$, rt. [b] In the presence of *p*-TSA. [c] Reaction at room temperature. [d] Reaction at reflux temperature. [e] Reaction conducted in toluene. [f] The diastereomeric ratio were estimated by NMR and/or GC. [g] Yields refer to isolated compounds after column chromatography. [h] Compound **3** and amine were used in a 1:1.1 ratio. [i] Untractable mixture.

As reported in Table 2, the expected piperidines **2** were obtained in all cases in good to excellent yields, except when reacting tricarbonyl substrates **3h** and **3j**. In the case of the diketone **3h** (Table 2, entries 15 and 16), the only product isolated after silica gel chromatography was racemic cyclohexanone **6**[17] (Scheme 2). Comparison of the physical and spectroscopic data for this compound with those reported in the literature[17] allowed to attribute a *cis* relative stereochemistry. This unexpected product was generated upon hydrolysis on silica gel of 1-oxo-4-azaspiro[4.5]decane **7** that was identified by NMR as the major product in the crude reaction mixture (characteristic quaternary carbon of the oxazolidine moiety at $\delta$ 95.5 ppm). We postulated that compound **7** was the result of an intramolecular aldolisation of the intermediate enamine formed upon addition of (*S*)-phenylglycinol on the carbonyl of the methyl ketone (Scheme 2).

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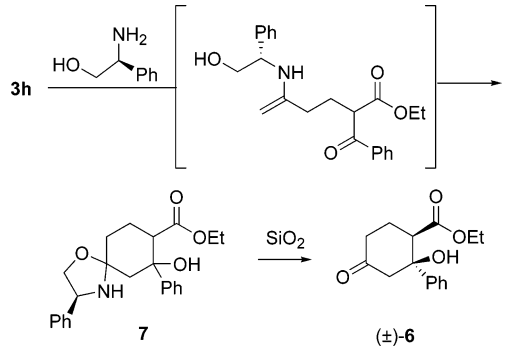
**SCHEME 2**



Concerning the chloromethyl ketone **3j**, reaction with (*S*)-phenylglycinol only resulted in an untractable mixture. This is probably due to side reactions on the chloromethyl ketone moiety.

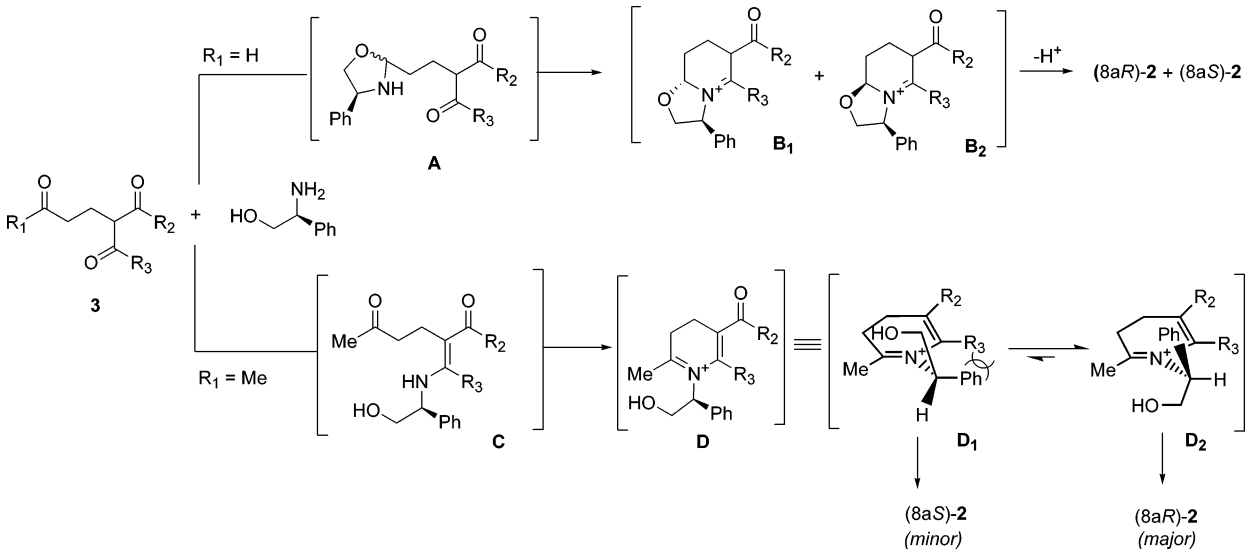
In the other cases, the expected piperidines **2** were obtained as separable mixtures of diastereomers at C-8a with poor diastereomeric excesses when using procedure A. Better diastereoselectivities were generally observed following procedure B, particularly for angular methyl-containing compounds (Table 2, entries 4, 8, and 12). In particular, X-ray data from the major isomers of oxazolidine **2b** and **2d** that were isolated as crystalline compounds allowed us to assign a (8a*R*) absolute stereochemistry to both derivatives. The same stereochemistry was attributed to the major isomer of compound **2f**, based on the comparison of NMR spectroscopic data. Indeed, the $^1$H NMR chemical shifts of the angular methyl of the major isomer of **2b**, **2d**, and **2f** were, respectively, at 1.44, 1.45, and 1.48 ppm. These singlets appeared deshielded compared to the corresponding one of the minor isomers of **2b**, **2d**, and **2f** at, respectively, 1.30, 1.29, and 1.33 ppm. This stereochemistry for the major isomers is in agreement with what we previously obtained for the synthesis of exocyclic $\beta$-enaminoesters **1**.[1]

Regarding the hydrogen-angular compounds, the reverse diastereoselectivity was observed. Here again, the configuration assignment of the two diastereoisomers were based on NMR data. The $^1$H and $^{13}$C NMR chemical shifts at C-8a for **2a**,**c**,**e**,**g**,**i** were, respectively, in the range 4.78−4.98 and 87.7−88.5 ppm for the major isomers and downfield in the range 5.23−5.07 and 89.1−89.5 ppm for the minor isomers. These values allowed us to assign the (8a*S*) absolute stereochemistry to the major isomers, in line with what was previously reported on similar oxazolidine piperidines.[18] X-ray analysis performed on the minor isomer of **2c** confirmed its (8a*R*) absolute stereochemistry. Moreover, no equilibrium between the two oxazolidine epimers at C-8a was detectable in the NMR spectra. This lack of epimerization at C-8a was probably as a consequence of the stabilizing effect of the $\beta$-enamino carbonyl moiety as already mentioned for analogous derivatives.[18]

These two opposite results concerning the stereochemistry at C-8a can be explained if one suppose that the first step of the process leading to compounds **2** depends on the nature of the substituent $R_1$ (Scheme 3). In the case of aldehydes ($R_1$ = H), the reaction would start with the initial condensation of (*S*)-phenylglycinol on the aldehyde moiety to lead to a diastereomeric mixture of oxazolidines **A**.[1] Subsequent attack of the hemiaminal nitrogen on the distal ketone group would give compounds **2** as a mixture of epimers via iminium ions $\mathbf{B_1}$ and $\mathbf{B_2}$.

Concerning the ketones ($R_1$ = Me and $R_3 \neq$ Ph), the observed high diastereoselectivities suggest that a different process has taken place. In this case, phenylglycinol would initially react on the activated ketone of the 1,3-dicarbonyl moiety to lead to enamine **C**. Intramolecular cyclization would then afford transiently iminium ion **D** as one of the two reactive conformations $\mathbf{D_1}$ and $\mathbf{D_2}$ that respectively would yield isomer (8a*S*)-**2** and (8a*R*)-**2** (Scheme 3). Due to the strong steric interaction between the phenyl group and the $R_3$ substituent that disfavors conformation $\mathbf{D_1}$, the intramolecular cyclization occurs preferentially via intermediate $\mathbf{D_2}$, which accounts for the preferred (8a*R*) diastereoselectivity. In contrast with these results, formation of cyclohexanone **6** from **3h** ($R_1$ = Me and $R_3$ = Ph) shows that the condensation of (*S*)-phenylglycinol first occurred on the methyl ketone

**SCHEME 3**



(Scheme 2), due to the known reduced reactivity of the benzoyl moiety compared to a methyl ketone.

In conclusion, we have developed an efficient access to new oxazolidines **2** by a two-step sequence, featuring a Michael reaction of symmetrical $\beta$-diketones or $\beta$-ketoesters with acrolein or methylvinyl ketone, followed by the condensation of (*S*)-phenylglycinol on the resulting tricarbonyl compounds. We believed that these highly functionalized compounds that we obtained in high yields will prove to be valuable intermediates for the synthesis of polysubtituted piperidine alkaloids. Further work along these lines, aimed at developing the synthetic applications of these polyfunctional heterocycles is under way in our laboratory.

## Experimental Section

**General Experimental Procedure for the Preparation of Compounds 3. General Procedure A.** Activated neutral Brockman I alumina was previously activated at 100 °C for 2 h. To an ice-cooled, stirred suspension of $Al_2O_3$ (10 g) was added compound **5** (1 mmol). Acrolein **4a** (1 mmol) was then added dropwise, and the reaction mixture was stirred for 10 min at 0 °C. The latter was then filtrered over a Celite pad and thoroughly washed with AcOEt. The organic layer was concentrated in vacuo. Purification by silica gel column chromatography yielded pure compound **3**.

**General Procedure B.** To a mixture of methyl vinyl ketone **4b** (1 mmol) and compound **5** (1 mmol) was added $Ni(acac)_2$ (0.01 mmol). The reaction mixture was stirred at 40 °C for 48 h and then purified by silica gel column chromatography to yield pure compound **3**. In the case of compounds **3d** and **3f** where the use of solvents was required (see Table 2), the latter was concentrated in vacuo prior to chromatography to give compounds **3**.

**General Experimental Procedure for the Preparation of Compounds 2. General Procedure A.** To a solution of compounds **3** (1 mmol) in $CH_2Cl_2$ (10 mL) were added (*S*)-phenylglycinol (2 mmol) and 4 Å molecular sieves (1 g). In the case of substrates **3b**,**d**,**f**,**h**,**j**, *p*-TSA (0.1 mmol) was equally added. The reaction mixture was stirred at room temperature for 24 h and then filtrated over a Celite pad, and the organic layer was concentrated in vacuo. Column chromatography on silica gel afforded the expected compounds **2**.

**General Procedure B.** To a solution of compounds **3** (1 mmol) in $CH_2Cl_2$ (10 mL) were successively added (*S*)-phenylglycinol (2 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (0.05 mmol), and $MgSO_4$ (0.3 mmol). The reaction mixture was stirred at room temperature for 24 h and filtrated. The organic layer was concentrated in vacuo, and column chromatography on silica gel afforded this expected compounds **2**.

**Supporting Information Available:** Characterization data for all obtained compounds.$^1$H and/or $^{13}$C NMR spectra of compounds **3**, **2,** and **6**. Tables of X-ray crystallographic data for compounds **(**8a*R*)-**2b**, (8a*R*)-**2c,** and **(**8a*R*)-**2d** as well as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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