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Novel Routes to Chiral 2-Alkoxy-5-/6-methoxycarbonylmethylidenepyrrolidines/-piperidines

Olivier David, Sandrine Calvet, François Chau,† Corinne Vanucci-Bacqué, Marie-Claude Fargeau-Bellassoued, and Gérard Lhommet*

Université P. et M. Curie, Chimie des Hétérocycles, UMR 7611, 4 Place Jussieu, 75252 Paris Cedex 05, France

lhommet@ccr.jussieu.fr

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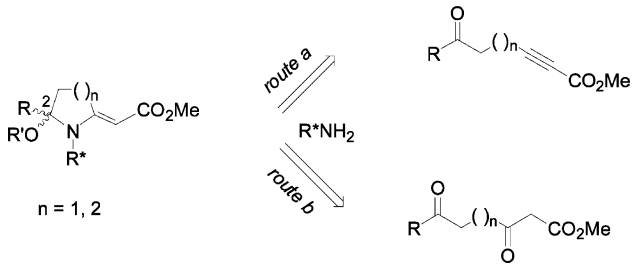
Abstract: We report the results of a study aimed at the diastereoselective synthesis of chiral 2-alkoxy-5-/6-methoxycarbonylmethylidenepyrrolidines/-piperidines by condensation of chiral amines onto ω-oxo alkynoates and ω-oxo β-keto esters.

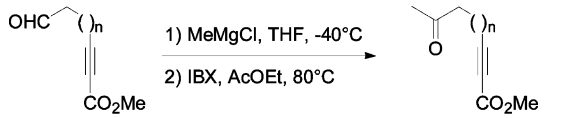
Saturated nitrogen-containing heterocycles bearing a β-enamino ester are versatile and useful synthetic intermediates for the preparation of natural products.[1] We have recently introduced a new strategy to synthesize such chiral pyrrolidines and piperidines by condensation of chiral amines on ω-halogeno alkynoates[2] or β-keto esters.[3] This approach constitutes a valuable alternative to the Eschenmoser procedure[4] in terms of workup, ease of purification, and sparing of the sacrificial chiral auxiliaries owing to their introduction in the late stage of the synthesis. However, this methodology only yields 2-monosubstituted pyrrolidines and piperidines. To access polysubstituted heterocycles, we were interested in increasing the synthetic potential of our target β-enamino esters by introducing an additional hemiaminal moiety which would act as a masked iminium ion allowing easy nucleophilic subtitutions at the α position of the nitrogen atom. We thus envisioned that reaction of ω-oxo alkynoates (route a) or ω-oxo β-keto esters (route b) with chiral amines would lead to such structures (Scheme 1). We now report the results of this study which features the reaction of (*S*)-1-phenylethylamine and (*S*)-phenylglycinol with alkynoates and β-keto esters possessing a terminal aldehyde or methyl ketone moiety.

We first considered synthesizing the target compounds starting from various ω-oxo alkynoates (Scheme 1, route a). The required aldehydes **1a** and **1b** were readily obtained starting from the corresponding terminal ω-hydroxy alkynes according to literature procedures.[5] The related methyl ketones **2a** and **2b**[6] were prepared in two steps from aldehydes **1a** and **1b** in, respectively, 50% and 54% overall yield, by chemoselective addition of methylmagnesium chloride on the aldehyde moieties followed by IBX oxidation[7] of the resulting crude alcohols (Scheme 2).

SCHEME 1



SCHEME 2



1a (n = 1)
1b (n = 2)

2a (n = 1) (50%)
2b (n = 2) (54%)

When reacted in methanol in the presence of 1 equiv of (*S*)-1-phenylethylamine and 4 Å molecular sieves, aldehyde **1a** afforded the expected chiral β-enamino ester **3** in 76% yield (Scheme 3) as the *E* configuration for the double bond[1a] and a 7:3 diastereomeric mixture at C-2 (determined by NMR analysis). Upon chromatography on silica gel, compound **3** tended to lose methanol leading, after aromatization, to the unprecedented chiral pyrrole **4**. Based on this observation, we anticipated that the condensation of (*S*)-1-phenylethylamine on **1a** would lead to **4** in the absence of methanol. Indeed, when conducted in refluxing toluene, the reaction afforded **4** in moderate 60% yield (Scheme 3). One can note indeed the formation of unidentified secondary products which lowered the isolated yield of **4**.

We assumed that this reaction had proceeded through the initial formation of an acyclic hemiaminal resulting from addition of the chiral amine on the carbonyl of the aldehyde, the most electrophilic center of the molecule, followed by dehydration to give an imine intermediate. In aprotic solvent, subsequent imine/enamine isomerization followed by addition of the nitrogen atom on the triple bond would afford the corresponding 2,3-dihydropyrrole that would rearrange to pyrrole **4** (Scheme 3). On the other hand, in the presence of methanol, addition of the solvent on the imine would afford two diastereomeric hemiaminals with little diastereofacial selectivity. Subsequent intramolecular attack of the nitrogen atom on the triple bond would then lead to the target molecule **3** with the observed poor stereoselectivity (Scheme 3). To

† Current address: Universtité Denis Diderot, Laboratoire de Pharmacochimie Moléculaire, 2 Place Jussieu,75251 Paris Cedex 05, France.

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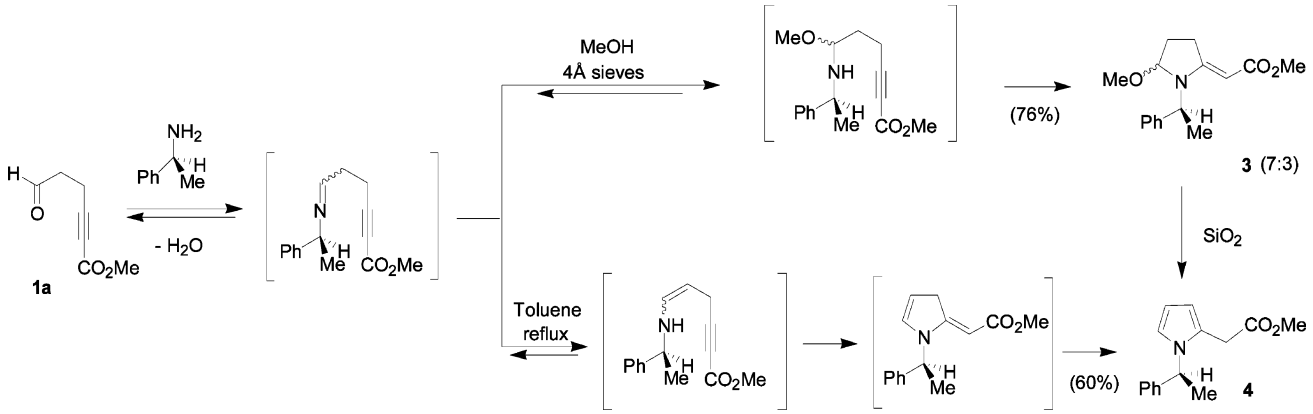
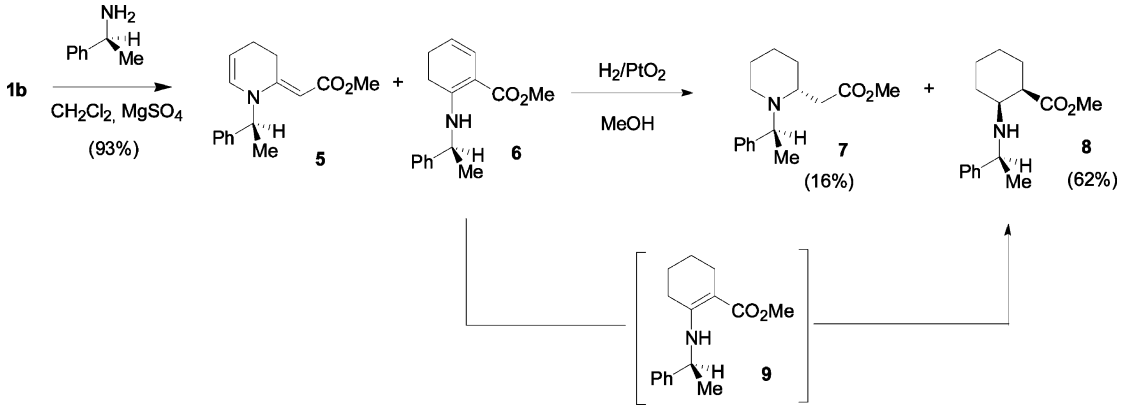
SCHEME 3



SCHEME 4



support these hypotheses, we conducted an experiment in which the progress of the reaction was followed in a tube by ^{1}H and ^{13}C NMR: **1a** was dissolved in deuteriochloroform and an equimolar amount of (*S*)-1-phenylethylamine was added. We immediately observed the disappearance of the aldehyde proton at δ 9.79 and the simultaneous appearance of a triplet at δ 7.80 ($J = 4$ Hz) assigned to the presence of the transient imine and of the signals characteristic of pyrrole **4**.

Concerning alkynoate **1b**, reaction in methanol in the presence of 4 Å molecular sieves did not give rise to the expected heterocycle at all but to an intractable complex mixture. At this stage, we envisaged running the reaction in nonalcoholic solvents in order to prepare, via a process similar to that leading to pyrrole **4**, the enaminopiperidine **5** that we expected to act as an iminium precursor (Scheme 4). However, when **1b** and the amine were reacted in CH_2Cl_2 at room temperature in the presence of $MgSO_4$ as a dehydrating agent, we identified not only the expected compound **5** but also more surprisingly cyclohexadiene **6** as the major product (Scheme 4). This mixture, obtained in 93% yield (ratio **5**/**6** 17:83 according to NMR and GC analysis), underwent degradation upon silica gel chromatography, which prevented clean isolation of **5** and **6**. A bulb-to-bulb distillation did not allow their isolation either. Therefore, we performed a catalytic hydrogenation on the crude mixture in order to secure the proposed structures. This reaction afforded the known compound **7**[8] arising from **5** and cyclohexane **8** arising from **6** in, respectively, 16% and 62% isolated yields (from the initial mixture). Progress of this hydrogenation by NMR showed that known cyclohexene **9**[9] was an intermediate toward **8** resulting from partial reduction. The stereochemistry of **8** was assigned as (1*R*,2*S*,α*S*) by comparison of its NMR data with those of the known analogue ethyl esters[10] for which all possible diastereomers have been described (Scheme 4).

As in the case of aldehyde **1a**, the obtention of compounds **5** and **6** can be rationalized by the initial formation of an intermediate imine **10** (Scheme 5) whose formation was clearly established during an NMR experiment. When equimolar amounts of **1b** and (*S*)-1-phenylethylamine were added in an NMR tube, we indeed observed the immediate disappearance of the aldehyde proton and carbon signals (δ 9.76 and 200.8) while the signals of the imine (δ 7.76 (t, $J = 4$ Hz) and 161.7) clearly appeared. At this stage, we assumed that imine **10** could afford enamino piperidine **5** according to a process similar to the one leading to **4** (see Scheme 3). In parallel, a second molecule of (*S*)-1-phenylethylamine would add to the activated triple bond of **10** to give rise to a transient enamine that would then react intramolecularly on the imine moiety to give a cyclic intermediate. Subsequent isomerization of the imine/enamine followed by elimination of (*S*)-1-phenylethylamine and

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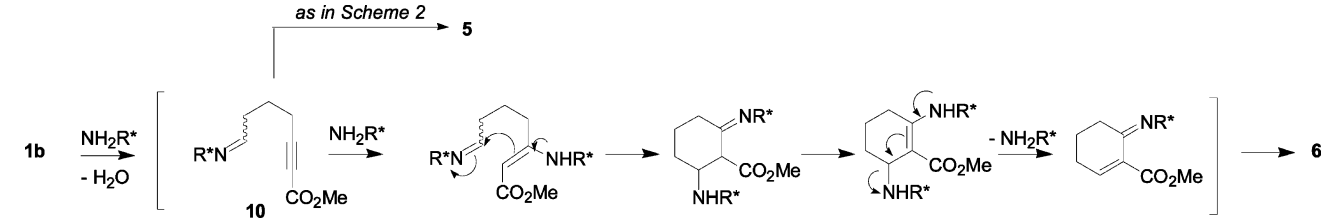
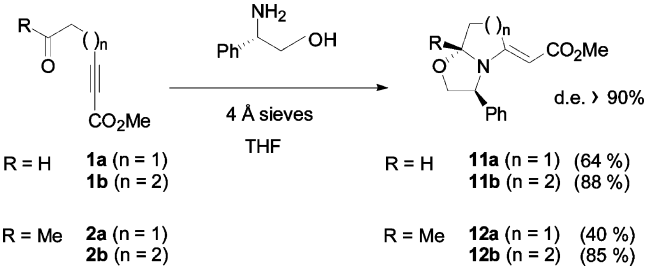
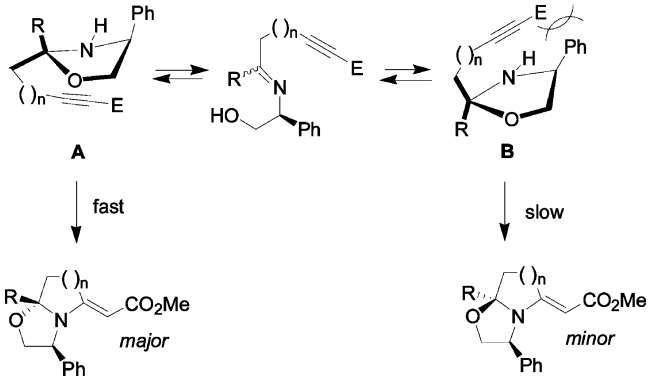
SCHEME 5



SCHEME 6



SCHEME 7



final prototropy would lead to compound **6.** This process, catalytic in amine, is summarized in Scheme 5.

As far as methyl ketones **2a** and **2b** were concerned, we obtained disappointing results: reactions with (*S*)-1-phenylethylamine in methanol only yielded intractable complex mixtures.

We next examined the reaction of *ω*-oxo alkynoates with (*S*)-phenylglycinol. This chiral amine that presented the advantage of bearing both an amine and an alcohol function was expected to lead to bicyclic structures upon intramolecular addition of the hydroxyl onto the intermediary imine. Indeed, when reacted in the presence of this amine and molecular sieves at room temperature, alkynoates **1a**,**b** and **2a**,**b** readily afforded the expected bicyclic heterocycles **11a**,**b** and **12a**,**b** in moderate yields for the pyrrolidines **11a** (64%) and **12a** (40%)[11] and in good yields for the piperidines **11b** (88%) and **12b** (85%) (Scheme 6). In all cases, excellent diastereoselectivity (de > 90% determined by GC and NMR analyses) at C-2 (now positions C-7a (n = 1) or C-8a (n = 2) of the bicycles) was observed. X-ray analyses performed on crystallized samples of the major isomers of **11a**, **11b**, and **12a** allowed us to assign a *E*-configuration for the double bonds and a 7a(*R*) or 8a(*R*) absolute configuration. As far as the methyl-substituted piperidine **12b** was concerned, the same 8a(*R*) configuration was ascribed for the major isomer after comparison of its spectroscopic data with that described by Munchhof and Meyers[12] for the same molecule, obtained via an Eschenmoser reaction from the appropriate thiolactam and subsequently used for the total synthesis of two piperidine alkaloids, (+)-pinidinone and (+)-monomorine.

Noteworthy were the excellent diastereomeric excesses observed in these cases by opposition to that obtained for **3**. We also followed by NMR the reaction of an equimolar amount of **1b** and (*S*)-phenylgycinol in deuteriochloroform. We rapidly observed the disappearance of the aldehyde signals and the appearance of the imine signals (δ 7.78 (t, J = 4 Hz) and 165.1) along with those characteristic of two oxazolidines in a 3:7 ratio (in particular, CH signals at δ 91.7 and 92.1). Based on these observations and in order to rationalize the stereochemical outcome of these reactions, we postulated that they proceeded through the initial formation of an intermediate imine that subsequently underwent an intramolecular addition of the hydroxyl of the *N*-(2-phenyl-1-hydroxy ethyl) moiety to afford a diastereomeric mixture of oxazolidines **A** and **B** (Scheme 7). The resulting hemiaminal nitrogen atom would then attack the activated triple bond. The observed diastereoselectity during this step (de > 90%) suggested that a dynamic kinetic resolution occurred during the final cyclization step, as previously proposed in the case of a diastereoselective preparation of oxazolopiperidones.[13] The preferential formation of the major isomer would be a consequence of a cyclization occurring faster from trans oxazolidine **A** and of the progressive isomerization of **B** into **A** driven by the cyclization of **A**. We supposed that oxazolidine **A** would allow an access of the nitrogen atom toward the triple bond more appropriate than the one possible for oxazolidine **B**.[14] In contrast with the previous reports on the lactam preparation,[13] the stereoselectivity observed in our case was independent of the nature of the R substituent (Scheme 7).

We then investigated the alternative route featuring *ω*-oxo *β*-keto esters as the substrates in place of *ω*-oxo alkynoates (Scheme 1, route b). The required aldehydes **15a**,**b** and methyl ketones **16a**[15] and **16b** (Scheme 8) were synthesized by ozonolysis of the corresponding known terminal alkenes **13a**,**b**[16] and **14a**,**b**[17] which in turn were readily obtained by condensation of the dianion of me-

(11) Pyrrolidine derivatives **11a** and **12a** are particularly sensitive to column chromatography which lowered their isolated yields.

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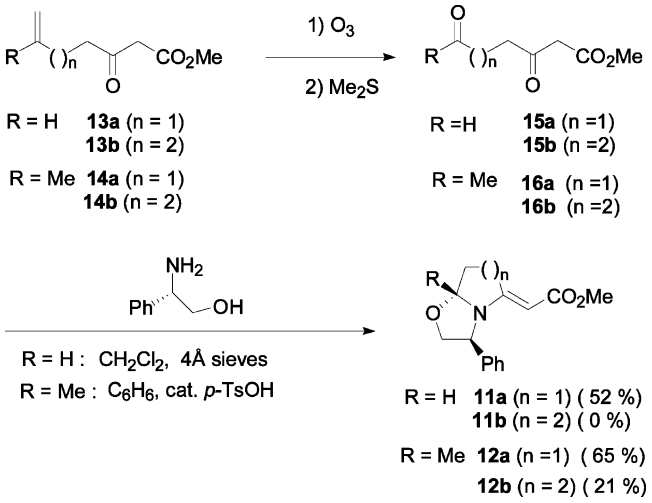
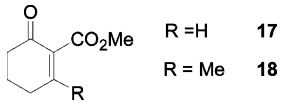
(15) For **16a**, see: Finch, N.; Fitt, J. J.; Hsu, I. H. C. *J. Org. Chem*. **1971**, *36*, 3191.

SCHEME 8



thylacetoacetate on the appropriate allylic or homoallylic halogenides. It was noteworthy that the intermediate ozonides were quite stable and even isolable, requiring long reaction time (48 h) and a large excess of dimethyl sulfide to be reduced. However, all attempts to isolate the resulting pure ω-oxo β-keto esters invariably failed, due to a spontaneous intramolecular aldolization−dehydration process that afforded undesirable cyclic enones during aqueous workup. This process was particularly easy and rapid in the case of **15b** and **16b** to give cyclohexenones **17**[18] and **18**.[19]



To overcome this stability issue, crude oxo derivatives containing residual dimethyl sulfoxyde were engaged as such in the next step. Upon reaction with (*S*)-1-phenylethylamine in methanol, we only obtained inextricable mixtures. On the other hand, reaction of **15a** and **16a** (n = 1) in the presence of (*S*)-phenylglycinol in appropriate solvents smoothly led to bicyclic β-enamino esters **11a** and **12a** in, respectively, 52% and 65% overall yields from the corresponding alkenes (Scheme 8). However, in the case of the sensitive aldehyde **15b** (n = 2), the sole identifiable product was again cyclohexenone **17**, whatever the reaction conditions. Concerning ketone **16b**, the expected bicyclic compound **12b** was isolated in only 21% yield along with undesired **18** in 24% yield. In all cases, the diastereoselectivity of these reactions was similar to that obtained from alkynoates (de > 90%) which was suggestive of a similar mechanistic process (Scheme 8).

In conclusion, we have developed valuable alternative routes to the Eschenmoser procedure for the synthesis of chiral 2-alkoxy-5-/6-methoxycarbonylidenepyrrolidines/-piperidines by condensation of chiral amines on ω-oxo alkynoates and β-keto esters. Our approach is particularly attractive for the diastereoselective preparation of bicyclic structures **11a**,**b** and **12a**,**b** from (*S*)-phenylglycinol. In particular, pyrrolidines **11a** and **12a** were obtained from ω-oxo β-keto esters very efficiently in terms of ease of access and cost of the starting materials whereas synthesis of piperidines **11b** and **12b** required the use of ω-oxo alkynoates as precursors. Further work to develop the synthetic applications of these polyfunctional heterocycles is underway in our laboratory.

Supporting Information Available: Experimental procedures and characterization data for all the new compounds. Tables of X-ray crystallographic data for compounds **11a**,**b** and **12a** as well as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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