ORGANIC LETTERS

2009
Vol. 11, No. 11
2249−2252

# Enantioselective Synthesis of β-(3-Hydroxypyrazol-1-yl) Ketones Using an Organocatalyzed Michael Addition Reaction

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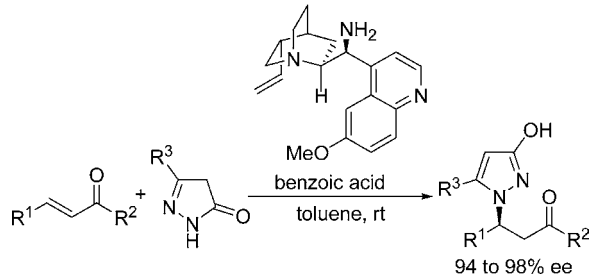
**Received March 14, 2009**

## ABSTRACT




**β-(3-Hydroxypyrazol-1-yl) ketones have been prepared in high yields and excellent enantioselectivities (94−98% ee) via a Michael addition reaction between 2-pyrazolin-5-ones and aliphatic acyclic α,β-unsaturated ketones using 9-*epi*-9-amino-9-deoxyquinine as the catalyst. These results account for the first example of an aza-Michael addition of the ambident 2-pyrazolin-5-one anion to a Michael acceptor.**

Pyrazole is an important pharmacophore. Compounds containing this moiety frequently exhibit various biological and pharmacological activities.[1] Among the pyrazole derivatives, 1-alkyl-3-hydroxyprazole derivatives are potent enzyme inhibitors[2a−d] and activators[2e] and have been widely used in antidiabetic,[2a−d] anticancer,[2f−h] anti-inflammatory,[2a] antipsychosis,[2a] insecticidal,[2i] and herbicidal[2j] studies. For example, *O*-pyrazole glucopyranoside and galactopyranoside derivatives, such as remogliflozin etabonate (Figure 1),[2d] are inhibitors of human sodium−glucose cotransporters 1 and 2 (SGLT1 and SGLT2) and may be used as antidiabetic agents.[2a−d,k]

1-Alkyl-3-hydroxyprazoles may be synthesized by condensing alkylhydrazines and β-substituted acetylenic esters[3a] or β-ketoesters.[3b] However, intrinsically these methods cannot be developed into an enantioselective synthesis for pyrazoles with chiral substituents.

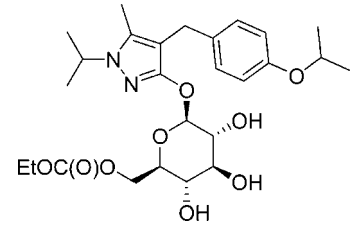



**Figure 1.** Remogliflozin etabonate (GlaxoSmithKline), an inhibitor of SGLT2 for the treatment of type 2 diabetes.

During our recent study of the organocatalyzed reaction of benzylidenemalononitriles and 3-methyl-2-pyrazolin-5-ones,[4] we envisaged that the anion of 3-methyl-2-pyrazolin-5-one should also be a suitable nucleophile for the conjugate

(1) For reviews, see: (a) Sondhi, S. M.; Dinodia, M.; Singh, J.; Rani, R. *Curr. Bioact. Comp.* **2007**, *3*, 91–108. (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Systems* **2002**, *6*, 52–98.

10.1021/ol900538q CCC: $40.75 
**Published on Web 05/05/2009**

addition to α,β-unsaturated ketones. It should be pointed out that the anion of 3-methyl-2-pyrazolin-5-one is an ambident nucleophile. There are ample examples that use it as a carbon nucleophile in carba-Michael addition reactions.[5] Moreover, the carba-Michael addition of this anion to aryl-substituted α,β-unsaturated ketones was also reported.[5a,b] However, to our knowledge, there is no report on its use as a nitrogen or an oxygen nucleophile in a Michael addition reaction. Herein we report the first example of an aza-Michael addition of the 3-methyl-2-pyrazolin-5-one anion[6] for a highly enantioselective synthesis of 1-alkyl-3-hydroxypyrazoles by using 9-*epi*-9-amino-9-deoxyquinine as the catalyst.

Primary amine-catalyzed conjugate addition to α,β-unsaturated ketones is an important strategy in organocatalysis.[7] Thus, some optically active primary amines (Figure 2) were adopted as the catalysts for the Michael addition of

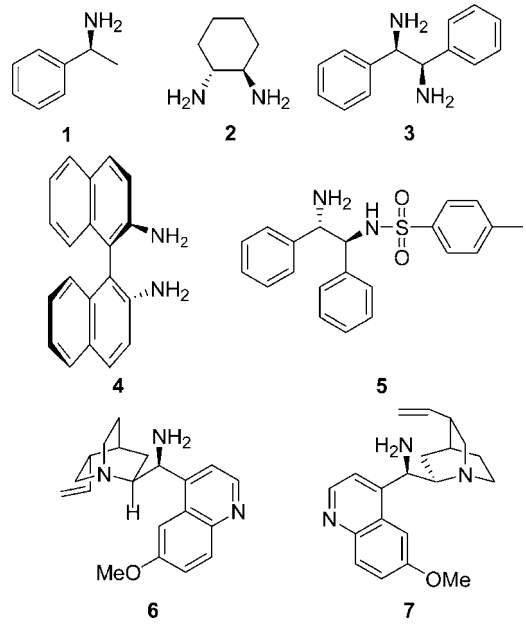
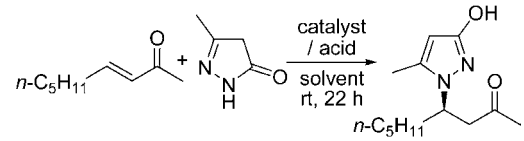



**Figure 2.** Catalysts screened for the aza-Michael addition of 3-methyl-2-pyrazolin-5-one (**9a**) to the α,β-unsaturated ketone **8a**.

3-methyl-2-pyrazolin-5-one (**9a**) to an α,β-unsaturated ketone **8a**. The results are listed in Table 1.

When 20 mol % of (*S*)-1-phenylethylamine (**1**) was used as the catalyst and 40 mol % of trifluoroacetic acid (TFA) was used as the cocatalyst in toluene at rt, the reaction of **8a** and **9a** produced a product in 30% yield (entry 1). The structure of this product was determined to be the 3-hydroxyprazole derivative **10a**. This is the first example of the addition of the anion of **9a** as a nitrogen nucleophile onto a Michael acceptor. The ee value of this aza-Michael product was determined to be 26%. Further screening some $C_2$-symmetric primary amines **2**−**4** revealed that higher yields of the product could be obtained; however, the ee values of the product remained low (entries 2−4). The monotosylated diamine **5** also leads to a poor enantioselectivity of the product (entry 5). To our pleasure, when 9-*epi*-9-amino-9-deoxyquinine (**6**) was used as the catalyst under these conditions, a good yield of 84% of the product was obtained, and the ee value was improved to 88% ee (entry 6). Catalyst **7**, the pseudoenantiomer of **6**, also yields the product in good yield, and a good ee value of 70% was obtained (entry 7). It

**Table 1.** Catalyst Screening and Optimization of the Reaction Conditions for the Michael Addition of 3-Methyl-2-pyrazolin-5-one (**9a**) to the α,β-Unsaturated Ketone **8a**[a]




**8a** **9a** **10a**

| entry | catalyst | solvent | acid additive | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **1** | toluene | TFA | 30 | 26[d] |
| 2 | **2** | toluene | TFA | 60 | 20[d] |
| 3 | **3** | toluene | TFA | 56 | 20[d] |
| 4 | **4** | toluene | TFA | 53 | 17[d] |
| 5 | **5** | toluene | TFA | 52 | 44 |
| 6 | **6** | toluene | TFA | 84 | 88 |
| 7 | **7** | toluene | TFA | 77 | 70[d] |
| 8 | **6** | toluene | *p*-TSA | 44 | 88 |
| 9 | **6** | toluene | $CH_3COOH$ | 57 | 92 |
| 10 | **6** | toluene | benzoic acid | 85 | 96 |
| 11 | **6** | benzene | benzoic acid | 79 | 96 |
| 12 | **6** | $Et_2O$ | benzoic acid | 70 | 96 |
| 13 | **6** | $CHCl_3$ | benzoic acid | 67 | 96 |
| 14 | **6** | THF | benzoic acid | 76 | 90 |
| 15 | **6** | $CH_2Cl_2$ | benzoic acid | 71 | 90 |
| 16 | **6** | $CH_3CN$ | benzoic acid | 52 | 76 |
| 17 | **6** | MeOH | benzoic acid | 7 | 37 |
| 18[e] | **6** | toluene | benzoic acid | 34 | 95 |
| 19[f] | **6** | toluene | benzoic acid | 69 | 95 |
| 20[g] | **6** | toluene | benzoic acid | 34 | 96 |

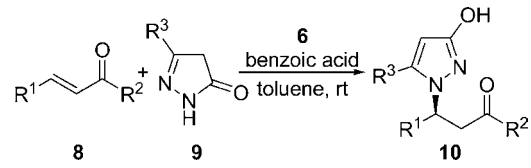
[a] Unless otherwise indicated, reactions were carried out with **8a** (0.1 mmol), **9a** (0.1 mmol), the catalyst (20 mol %), and the acid additive (40 mol %) in the specified solvent (0.6 mL) at rt. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC using a ChiralCel OD-H column. [d] The *S* enantiomer was obtained as the major product. [e] 10 mol % of catalyst **6** and 40 mol % of benzoic acid were used. [f] 20 mol % of catalyst **6** and 20 mol % of benzoic acid were used. [g] 10 mol % of catalyst **6** and 20 mol % of benzoic acid were used.

(2) (a) Cuberes-Altisent, R.; Holenz, J. PCT Int. Appl. WO2007098953, 2007;*Chem. Abstr.* **2007**, *147*, 301168. (b) Teranishi, H.; Fushimi, N.; Yonekubo, S.; Shimizu, K.; Shibazaki, T.; Isaji, M. PCT Int. Appl. WO2004014932, 2004;*Chem. Abstr.* **2004**, *140*, 199632. (c) Washburn, W. N. PCT Int. Appl. WO2003020737, 2003; *Chem. Abstr.* **2003**, *138*, 221784. (d) Shiohara, H.; Fujikura, H.; Fushimi, N.; Ito, F.; Isaji, M. PCT Int. Appl. WO 2002098893, 2002;*Chem. Abstr.* **2003**, *138*, 24917. (e) Selwood, D. L.; Brummell, D. G.; Budworth, J.; et al. *J. Med. Chem.* **2001**, *44*, 78–93. (f) Baraldi, P. G.; Nunez, M. d. C.; Tabrizi, M. A.; De Clercq, E; Balzarini, J.; Bermejo, J.; Estevez, F.; Romagnoli, R. *J. Med. Chem.* **2004**, *47*, 2877–2886. (g) Brana, M. F.; Gradillas, A.; Ovalles, A. G.; Lopez, B.; Acero, N.; Llinares, F.; Mingarro, D. M. *Bioorg. Med. Chem.* **2006**, *14*, 9–16. (h) Alterio, D.; Jereczek-Fossa, B. A.; Fiore, M. R.; Piperno, G.; Ansarin, M.; Orecchia, R. *Anticancer Res.* **2007**, *27*, 1105–1125. (i) Hughes, K. A.; Lahm, G. P.; Selby, T. P. PCT Int. Appl. WO2004046129, 2004;*Chem. Abstr.* **2004**, *141*, 23526. (j) Ohno, R.; Watanabe, A.; Matsukawa, T.; Ueda, T.; Sakurai, H.; Hori, M.; Hirai, K. *J. Pesticide Sci.* **2004**, *29*, 15–26. (k) Fujimori, Y.; Katsuno, K.; Nakashima, I.; Ishikawa-Takemura, Y.; Fujikura, H.; Isaji, M. *J. Pharm. Exp. Therap.* **2008**, *327*, 268–276. For a review, see: Washburn, W. N. *J. Med. Chem.* **2009**, *52*, 1785–1794.

should be pointed out that the major enantiomer obtained with catalysts **5** and **6** is opposite that obtained with catalysts **1**−**4** and **7**. Thus, this screening identified catalyst **6** as the best catalyst for this reaction. Next, the acid cocatalyst was screened. *p*-Toluenesulfonic acid (*p*-TSA) was found to generate the same ee value of the product as TFA, but it diminished the yield of the product (entry 8). Acetic acid generated a slightly better ee value of 92%; nevertheless, the yield was much lower than that obtained with TFA (entry 9). Benzoic acid was the best cocatalyst because a good yield of 85% of product was achieved and the ee value of the product was increased to 96% (entry 10). Further optimization of the solvent revealed this excellent ee value may also be obtained from benzene, $Et_2O$, and $CHCl_3$ (entries 11−13), albeit with slightly lower yields of the product; however, THF, $CH_2Cl_2$, $CH_3CN$, and MeOH (entries 14−17) are worse solvents since the ee values and yields obtained were lower. Thus, toluene was identified as the best solvent for this reaction. Reducing the catalyst loading to 10 mol % (entry 18), reducing the benzoic acid loading to 20 mol % (entry 19), or reducing the loadings of both the catalyst and the cocatalyst (entry 20) all led to reduced yields of the product, whereas the asymmetric induction was not affected. While lowering the reaction temperature to 0 °C shows no effect on the enantioselectivity, elevating the reaction temperature to 40 °C leads to a drop of the ee value to 90% (data not shown).

The scope and limitations of this reaction were then studied under the optimized conditions (20 mol % loading of catalyst **6** and 40 mol % loading of benzoic acid in toluene at rt). The results are collected in Table 2. As shown by the results in Table 2, the chain length of the group connected to the C−C double bond ($R^1$) of the unsaturated ketone **8** has no effect on the enantioselectivity and reactivity of this reaction because similarly good results were obtained from methyl to *n*-hexyl derivatives (entries 1−5). In addition, excellent results were obtained when the size of the $R^1$ was increased to an isopropyl group (entry 6). However, when $R^1$ is a phenyl group, a mixture of unidentified products was obtained (data not shown). Nonetheless, if the phenyl group

**Table 2.** Aza-Michael Addition of 2-Pyrazolin-5-ones to α,β-Unsaturated Ketones Catalyzed by **6**[a]




**8** **9** **10**

| entry | $R^1$ | $R^2$ | $R^3$ | **10** | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | *n*-Pent | Me | Me | **a** | 22 | 85 | 96 |
| 2 | Me | Me | Me | **b** | 24 | 85 | 96 |
| 3 | Et | Me | Me | **c** | 26 | 87 | 96 |
| 4 | *n*-Bu | Me | Me | **d** | 25 | 84 | 96 |
| 5 | *n*-Hex | Me | Me | **e** | 25 | 81 | 94 |
| 6 | *i*-Pr | Me | Me | **f** | 27 | 79 | 98 |
| 7 | $PhCH_2$ | Me | Me | **g** | 23 | 84 | 94 |
| 8 | $Ph(CH_2)_2$ | Me | Me | **h** | 24 | 78 | 94[d] |
| 9 | Me | Et | Me | **i** | 25 | 79 | 97 |
| 10 | Me | *n*-Pr | Me | **j** | 25 | 81 | 98 |
| 11 | Me | Me | Et | **k** | 26 | 86 | 96 |
| 12 | Et | Me | Et | **l** | 24 | 82 | 96 |

[a] Unless otherwise indicated, reactions were carried out with **8** (0.1 mmol), **9** (0.1 mmol), catalyst **6** (20 mol %), and benzoic acid (40 mol %) in toluene (0.6 mL) at rt. [b] Yield of isolated product after column chromatography. [c] Unless otherwise indicated, the ee values were determined by HPLC analysis using a ChiralCel OD-H column. [d] Determined by HPLC analysis using a Chiralpak AS column.

is not directly attached to the double bond, such as in the benzyl or the 2-phenylethyl groups, high yields and excellent ee values of the desired products were again obtained (entries 7 and 8). Similarly, the group ($R^2$) connected the carbonyl group of **8** has no influence on the enantioselectivity of this reaction (entries 2, 9, and 10). Nevertheless, if $R^2$ is a phenyl group, such as in *trans*-chalcone and *trans*-crotonophenone, the reaction failed to proceed (data not shown), probably due to the low reactivity of such aromatic ketones. A cyclic enone, cyclohex-2-enone, produces a complex mixture of unidentified products (data not shown). Excellent ee values and good yields were also obtained when the alkyl group on the 2-pyrazolin-5-one was changed from a methyl group to an ethyl group (entries 11 and 12).

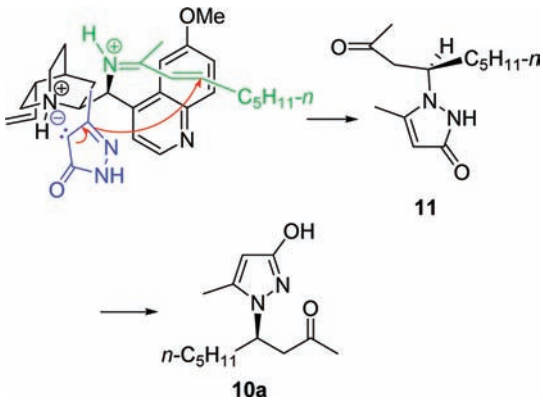
The absolute configuration of the major enantiomers formed in this reaction was determined by X-ray crystallographic analysis of the product **10d** (Table 2, entry 4).[8,9] According to the X-ray data, in the solid state, two molecules of the same product form two complementary intermolecular hydrogen bonds between the 3-hydroxy group of one molecule and the 2-nitrogen atom of the other. The absolute configuration of the carbon stereogenic center formed during the reaction is determined to be *R*.[9]

The reaction may be explained by the proposed transition state in Scheme 1. The enone **8a** reacts with catalyst **6** to form an iminium intermediate under the action of the acid

(3) (a) Hamper, B. C.; Kurtzweil, M. L.; Beck, J. P. *J. Org. Chem.* **1992**, *57*, 5680–5686. (b) Carpino, L. A. *J. Am. Chem. Soc.* **1958**, *80*, 599–601.
(4) Gogoi, S.; Zhao, C.-G. *Tetrahedron Lett.* **2009**, *50*, 2252–2255.
(5) For the cojugate addition to α,β-unsaturated aryl ketones, see: (a) Etman, H. A.; El-Ahl, A. S.; Metwally, M. A. *Arch. Pharm. Res.* **1994**, *17*, 278–280. (b) Metwally, S. A. M.; Younes, M. I.; Nour, A. M. *Bull. Faculty Sci., Assiut Univ.* **1986**, *15*, 1–9. (c) For a summary, see ref 4.
(6) For related examples, see: (a) Moran, J.; Dornan, P.; Beauchemin, A. M. *Org. Lett.* **2007**, *9*, 3893–3896. (b) Han, X. *Tetrahedron Lett.* **2007**, *48*, 2845–2849.
(7) For some leading examples of primary amine-catalyzed Michael additions, see: (a) Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112–8115. (b) Li, P.; Wen, S.; Yu, F.; Liu, Q.; Li, W.; Wang, Y.; Liang, X.; Ye, J. *Org. Lett.* **2009**, *11*, 753–756. (c) Kang, T.-R.; Xie, J.-W.; Du, W.; Feng, X.; Chen, Y.-C. *Org. Biomol. Chem.* **2008**, *6*, 2673–2675. (d) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135. (e) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425–3428. (f) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071. (g) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389–392. (h) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413–415. (i) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967–1969. (j) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599–602.

(8) For details, see the Supporting Information.
(9) CCDC 721869 contains the supplementary crystallographic data for **10d**. These data can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

**Scheme 1.** Proposed Transition State of the Aza-Michael Addition Reaction




cocatalyst. Simultaneously, catalyst **6** also deprotonates 3-methyl-2-pyrazolin-5-one (**9a**) to give the anionic intermediate. Due to ionic interactions, this anion and the quinuclidine ammonium form a tight complex (Scheme 1). The attack of the nitrogen site of the 3-methyl-2-pyrazolin-5-one anion onto the α,*β*-unsaturated iminium from below yields the intermediate **11** after hydrolysis, which tautomerizes to yield the product **10a**. Although it is known that the 3-methyl-2-pyrazolin-5-one anion adds to α,*β*-unsaturated ketones as a carbon nucleophile under basic conditions,[5a,b] under our mild acidic conditions, the nitrogen site instead of the carbon site adds to the activated Michael acceptor probably because the nitrogen site is more nucleophilic.

In summary, we have observed the first example of an aza-Michael addition of the 2-pyrazolin-5-one anion to α,*β*-unsaturated acyclic aliphatic ketones. By using 9-*epi*-9-amino-9-deoxyquinine as the catalyst and benzoic acid as the cocatalyst, high enantioselectivity (94−98% ee) and good yields have been achieved for the direct synthesis of *β*-(3-hydroxypyrazol-1-yl) ketones.

**Acknowledgment.** This research is financially supported by the Welch Foundation (Grant No. AX-1593) and partly by the National Institute of General Medical Sciences (Grant No. 1SC1GM082718-01A1), for which the authors are most grateful. We also thank Dr. William Haskins and the RCMI Proteomics Core (NIH G12 RR013646) at UTSA for assistance with HRMS experiment design, sample preparation, data collection, and results interpretation and Dr. Hadi Arman (UTSA) for help with the X-ray analysis.

**Supporting Information Available:** Experimental procedures, compound characterization data, and NMR spectra for new compounds, HPLC analysis spectra, and HRMS analysis spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900538Q