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Enantioselective Synthesis of β -(3-Hydroxypyrazol-1-yl)ketones Using An Organocatalyzed Michael Addition Reaction

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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-hydroxypyrazole derivatives are potent enzyme inhibitors^{2a–d} and activators,^{2e} and have been widely used in anti-diabetic,^{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-hydroxypyrazoles 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.

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 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 using 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

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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 at charge via the Internet at <http://pubs.acs.org>.

ketones was also reported.^{5a–b} However, to our knowledge, there is no report on using it as a nitrogen or an oxygen nucleophile in a Michael addition reaction. Herein we wish to report the first example of an aza-Michael addition of the 3-methyl-2-pyrazolin-5-one anion⁶ 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 3-methyl-2-pyrazolin-5-one (**9a**) to an α,β -unsaturated ketone **8a**. The results are listed in Table 1.

When 20 mol % (*S*)-1-phenylethylamine (**1**) was used as the catalyst and 40 mol % trifluoroacetic acid (TFA) was used as the co-catalyst 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-hydroxypyrazole 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 pseudo enantiomer of **6**, also yields the product in good yield and a good ee value of 70% ee was obtained (entry 7). It should be pointed out that the major enantiomer obtained with catalysts **5** and **6** is opposite to that obtained with catalysts **1–4** and **7**. Thus, this screening identified catalyst **6** as the best catalyst for this reaction. Next the acid co-catalyst 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 slightly better ee value of 92%; nevertheless, the yield was much lower than that obtained with TFA (entry 9). Benzoic acid came out to be the best co-catalyst, 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, Et₂O, and CHCl₃ (entries 11–13), albeit with slightly less yields of the product; however, THF, CH₂Cl₂, CH₃CN, 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), or reducing the benzoic acid loading to 20 mol % (entry 19), or reducing the loadings of both the catalyst and the co-catalyst (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).

Then the scope and limitations of this reaction were 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). Also 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 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 7–8). Similarly, the group (R^2) connected the carbonyl group of **8** has no influence on the enantioselectivity of this reaction (entries 2, 9–10). 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 11–12).

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 co-catalyst. 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 co-catalyst, high enantioselectivity (94–98% ee) and good yields have been achieved for the direct synthesis of β -(3-hydroxypyrazol-1-yl)ketones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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8. For details, please 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.

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

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

Scheme 1.

Proposed Transition State of the Aza-Michael Addition Reaction

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

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	<i>p</i> -TSA	44	88
9	6	toluene	CH ₃ COOH	57	92
10	6	toluene	benzoic acid	85	96
11	6	benzene	benzoic acid	79	96
12	6	Et ₂ O	benzoic acid	70	96
13	6	CHCl ₃	benzoic acid	67	96
14	6	THF	benzoic acid	76	90
15	6	CH ₂ Cl ₂	benzoic acid	71	90
16	6	CH ₃ CN	benzoic acid	52	76
17	6	MeOH	benzoic acid	7	37
18 ^{ef}	6	toluene	benzoic acid	34	95

entry	catalyst	solvent	acid additive	yield (%) ^b	ee (%) ^c
19 ^g	6	toluene	benzoic acid	69	95
20	6	toluene	benzoic acid	34	96

^aUnless 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.

^bYield of isolated product after column chromatography.

^cDetermined by HPLC using a ChiralCel OD-H column.

^dThe *S* enantiomer was obtained as the major product.

^e10 mol % of catalyst **6** and 40 mol % of benzoic acid were used.

^f20 mol % of catalyst **6** and 20 mol % of benzoic acid were used.

^g10 mol % of catalyst **6** and 20 mol % of benzoic acid were used.

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

entry	R ¹	R ²	R ³	10	time (h)	yield (%) ^b	ee ^c (%)
1	<i>n</i> -Pent	Me	Me	a	22	85	96
2	Me	Me	Me	b	24	85	96
3	Ft	Me	Me	c	26	87	96
4	<i>n</i> -Bu	Me	Me	d	25	84	96
5	<i>n</i> -Hex	Me	Me	e	25	81	94
6	<i>i</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	Ft	Me	i	25	79	97
10	Me	<i>n</i> -Pr	Me	j	25	81	98
11	Me	Me	Ft	k	26	86	96
12	Ft	Me	Ft	l	24	82	96

^aUnless 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.

^bYield of isolated product after column chromatography.

^cUnless otherwise indicated, the ee values were determined by HPLC analysis using a ChiralCel OD-H column.

^dDetermined by HPLC analysis using a Chiralpak AS column.