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Mannich Reactions of Carbohydrate Derivatives with Ketones to Afford Polyoxy-Functionalized Piperidines

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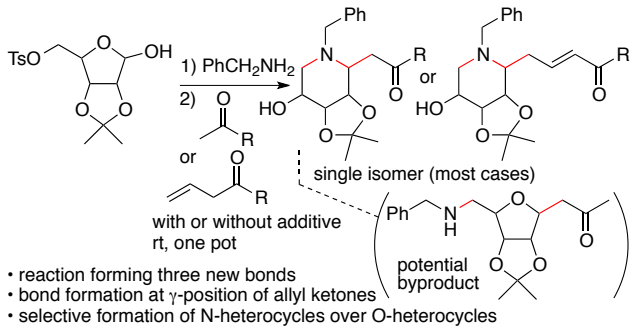
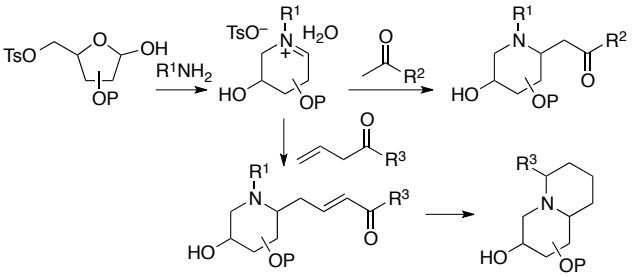


ABSTRACT: Mannich reactions of carbohydrate derivatives with ketones that afford polyoxy-functionalized piperidines are reported. Ketone nucleophiles (enamines/enolates) were generated in the presence of the amines used for the formation of the iminium ions of sugar derivatives with or without an additive. Conditions to preferentially generate piperidine derivatives rather than tetrahydrofurans were identified. Products from the reactions of allyl ketones were readily transformed to bicyclic piperidines.

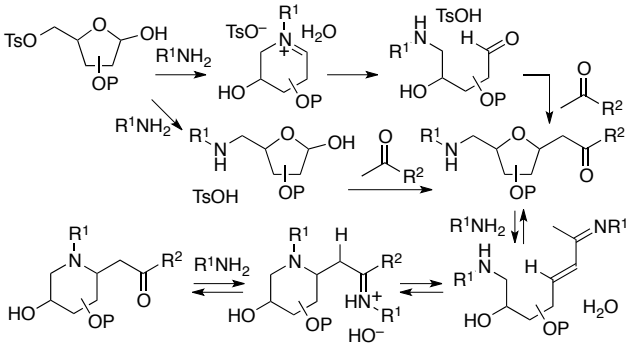
Polyoxy-functionalized piperidine derivatives are found in pharmaceuticals, probes, and their building blocks.[1] Therefore, the development of methods for the synthesis of polyoxy-functionalized piperidine derivatives is of interest in drug discovery and related areas. Whereas various reaction methods for the synthesis of piperidine derivatives have been reported, most provide piperidines bearing only mono- and di-substitutions on the carbons of the piperidine rings.[2] For the synthesis polyoxy-functionalized piperidines, strategies that are different from those used for the synthesis of simple piperidines are required. Here we report the Mannich reactions of sugar derivatives with ketones that afford polyoxy-substituted piperidine derivatives bearing ketone groups (Scheme 1).

Piperidines bearing ketone functional groups are used for the synthesis of various functionalized piperidine derivatives.[2a-g,3] The introduction of a substituent bearing a ketone group to a piperidine often requires several steps.[2b,d,e] To synthesize simple piperidines bearing ketone group moieties, Mannich-type reactions of simple cyclic imines and of simple cyclic nitrones with ketones have been reported.[2a,c] These reactions cannot provide polyoxy-substituted piperidines, however. We reasoned that the use of ketones as nucleophiles in the reactions with the iminium ions generated in situ from sugar derivatives would provide a direct route to ketone- and polyoxy-functionalized piperidine derivatives (Scheme 1). Whereas iminium ions derived from sugar derivatives have been used in reactions with various nucleophiles,[4] reactions with ketones that provide piperidines have not been realized previously.[5]

Scheme 1. Mannich reactions of sugar derivatives with ketones that afford polyoxy-functionalized piperidine derivatives.



Scheme 2. Potential side reactions that may occur during the Mannich reactions.

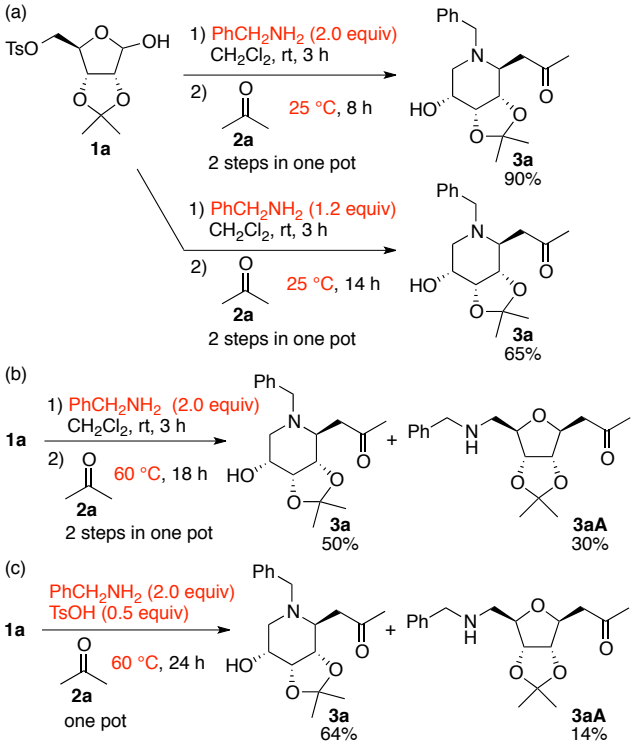


Compounds bearing primary amines have been used as catalysts and components of catalyst systems for the reactions

involving ketone nucleophiles under certain conditions.[6] Therefore, we hypothesized that amines (for example, R^1NH_2 = benzylamine in Scheme 1) used for the formation of the iminium ions would also act as catalysts for the Mannich reactions of the iminium ions with ketones via the formation of enamines/enolates of ketones under appropriate conditions (Scheme 1). When sugar derivatives are used as reactants, there are potential side reactions that must be avoided to afford piperidines (Scheme 2). A hydroxy group can be generated from the hemiacetal group of the sugar molecule during the Mannich reaction, and the hydroxy group may lead to oxa-cyclization, which results in the formation of tetrahydrofuran derivative. Formation of the iminium ions in situ cogenerates water molecules, and these water molecules may hydrolyze the iminium ions. Subsequent reaction of the aldehyde group with the ketone followed by oxa-cyclization may also result in the formation of tetrahydrofuran derivatives. Incomplete iminium ion formation may also provide the tetrahydrofuran derivatives. Interconversion between the piperidine derivatives and the tetrahydrofuran derivatives may also occur. In fact, previously reported reactions of iminium ions derived from sugar derivatives with ketones afforded tetrahydrofuran derivatives.[7]

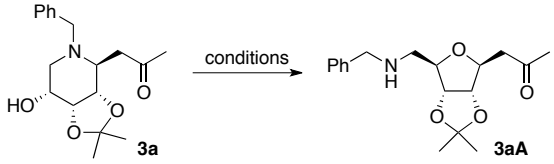
To identify conditions suitable for the formation of piperidine derivatives, we first examined the reaction of D-ribose derivative **1a**[4b-d] with acetone (**2a**) to afford piperidine derivative **3a** (Scheme 3). When an iminium ion was formed from **1a** (1.0 equiv) with benzylamine (2.0 equiv) in situ and was reacted with acetone at room temperature (25 °C) in one pot, product **3a** was obtained in 90% from **1a** as a single diastereomer (Scheme 3a). The use of less benzylamine also afforded **3a**; for example, in the reaction with 1.2 equiv of benzylamine to **1a**, product **3a** was obtained in 65% after 14 h (Scheme 3a). Reactions at 60 °C led the formation of tetrahydrofuran deriative **3aA**[7] as well as piperidine derivative **3a** (Scheme 3b,c).

Scheme 3. Mannich reaction of **1a** with **2a** to afford **3a**.



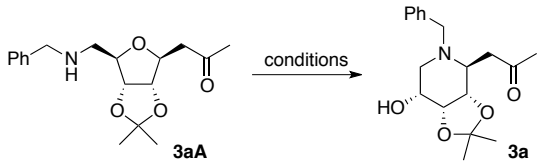
Next, the stability of **3a** and the conversions of **3a** to **3aA** and of **3aA** to **3a** were analyzed (Tables 1 and 2). Whereas **3a** was unchanged in toluene at 60 °C for at least 24 h in the absence of amine or acid (Table 1, entry 1), heating of **3a** at 60 °C in the presence of TsOH, benzylamine, or pyrrolidine resulted in the formation of **3aA** in significant yields (Table 1, entries 2, 4, 6). Piperidine derivative **3a** was stable (<5% conversion) at 25 °C in the presence of TsOH, benzylamine, pyrrolidine, or DBU at least for 24 h (Table 1, entries 3, 5, 7, and 8).

Table 1. Stability of **3a** and conversion of **3a** to **3aA**.



entry	conditions	results
1	60 °C in toluene, 24 h	**3a** unchanged
2	TsOH (0.5 equiv), 60 °C in $CHCl_3$, 24 h	**3aA** 80% (isolated)
3	TsOH (0.5 equiv), 25 °C in CH_2Cl_2, 24 h	**3a** >95% unchanged
4	$PhCH_2NH_2$ (1.0 equiv), 60 °C in toluene, 2 h	**3aA** 85% (isolated)
5	$PhCH_2NH_2$ (1.0 equiv), 25 °C in $CDCl_3$, 48 h	**3a** >95% unchanged
6	pyrrolidine (0.2 equiv), 60 ° C in $CDCl_3$, 4 h	**3a**:**3aA** = 1:1
7	pyrrolidine (0.2 equiv), 25 ° C in $CDCl_3$, 48 h	**3a** >95% unchanged
8	DBU (0.3 equiv), 25 ° C in $CDCl_3$, 24 h	**3a** >95% unchanged

Table 2. Stability of **3aA** and conversion of **3aA** to **3a**.



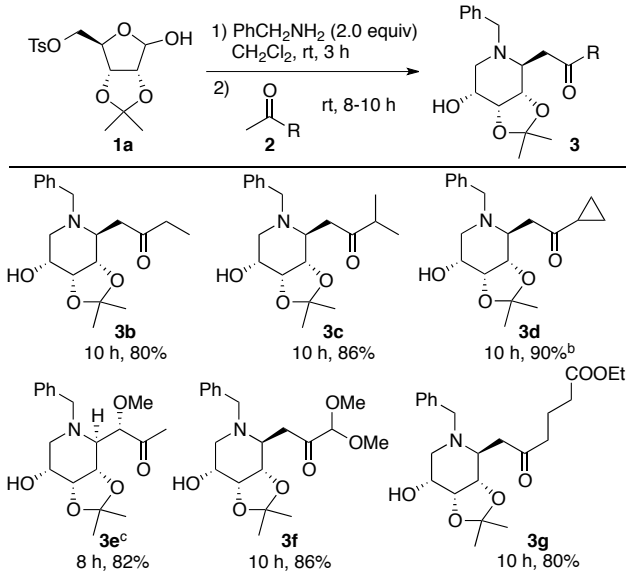
entry	conditions	results
1	pyrrolidine (0.2 equiv), 25 ° C in $CDCl_3$	**3a**:**3aA** = 3:7 at 15 h, 1:1 at 40 h
2	pyrrolidine (0.5 equiv), 25 ° C in CH_2Cl_2, 20 h	**3a** 45% (isolated)
3	pyrrolidine (0.2 equiv), 60 ° C in $CDCl_3$	**3a**:**3aA** = 1:3 at 2 h, 1:1 at 4 h
4	$PhCH_2NH_2$ (0.2 equiv), 25 ° C in CH_2Cl_2, 48 h	**3aA** >90% unchanged
5	$PhCH_2NH_2$ (1.0 equiv), 25 ° C in CH_2Cl_2, 48 h	**3a**:**3aA** = 2:3
6	TsOH (0.5 equiv), 25 ° C in CH_2Cl_2, 24 h	**3aA** >90% unchanged
7	$PhCH_2NH_2$ (0.5 equiv)-TsOH (0.2 equiv), 25 ° C in CH_2Cl_2, 24 h	**3a**:**3aA** = 1:1
8	$PhCH_2NH_2$ (1.0 equiv)-DBU (0.5 equiv), 25 ° C in CH_2Cl_2, 14 h	**3a**:**3aA** = ~1:1
9	DBU (0.5 equiv), 25 ° C in CH_2Cl_2, 24 h	**3a**:**3aA** = ~1:1
10	100 °C, toluene, 2 h	**3a**:**3aA** = 3:1

11	TsOH (0.5 equiv), 60 ° C in CH_2Cl_2	**3a**:**3aA** = 1:3 at 2 h, 4 h, and 24 h

In contrast, furan derivative **3aA** was partly converted to **3a** at 25 °C in the presence of pyrrolidine (Table 2, entries 1 and 2). Heating of **3aA** at 60 °C or at 100 °C also caused partial formation of **3a** in the presence and absence of pyrrolidine or TsOH (Table 2, entries 3, 10, and 11). At 25 °C, benzylamine also isomerized **3aA** to **3a**, depending on its loading amount (Table 2, entries 4 and 5). In the presence benzylamine-TsOH, benzylamine-DBU, or DBU alone, the formation of **3a** from **3aA** was also observed at 25 °C (Table 2, entries 7-9). The isomerization of **3aA** to **3a** in the presence of benzylamine (Table 2, entries 4 and 5) at 25 °C was significantly slower than the formation of **3a** in the ketone reaction step of the reaction of **1a** shown in Scheme 3a. Thus, in terms of yield of piperidine derivative **3a**, the direct formation of **3a** from **1a** as shown in Scheme 3a was superior to the isomerization of **3aA** to **3a**. To avoid the formation of **3aA**, it was necessary to conduct the reaction with the ketone at 25 °C (no heating).

Using conditions of Scheme 3a, piperidine derivatives **3** were synthesized using various alkyl and functionalized alkyl ketones **2** (Scheme 4). For the reaction with 2-butanone, the C-C bond formation occurred at the methyl group of the ketone (formation of **3b**). In the reaction with methoxyacetone, the C-C bond formed at the methoxy-substituted carbon (formation of **3e**).

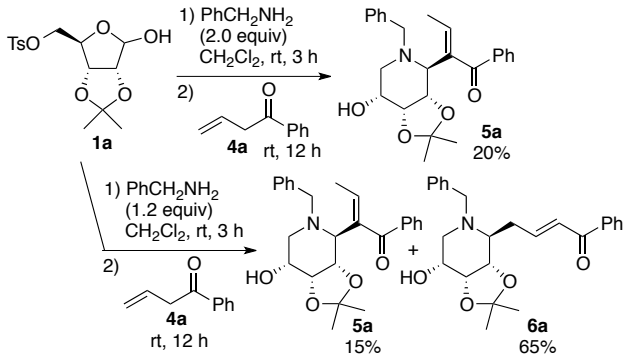
Scheme 4. Mannich reactions to afford **3** from **1a**.[a]



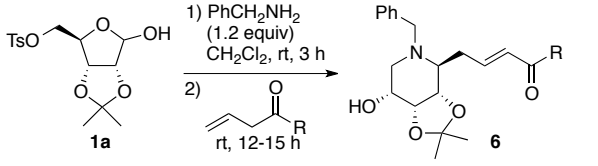
[a] Conditions: D-Ribose tosylate **1a** (0.45 mmol, 1.0 equiv) and $PhCH_2NH_2$ (2.0 equiv) in CH_2Cl_2 (2.0 mL) at rt (25 °C) for 3 h; then addition of ketone **2** (5.0 equiv). Products **3** were isolated as single diastereomers (dr >20:1). [b] L-Ribose-derived starting material was used and the product was an opposite enantiomer of the structure shown. [c] The stereochemistry of the metoxy-substituted carbon is tenetatively assigned (see Supporting Information).

In the case of the reaction of allyl phenyl ketone (**4a**),[8] the use of 2.0 equiv of benzylamine (relative to **1a**) resulted in the formation of product **5a** in 20%; the C-C bond formation occurred at the α-position of the allyl ketone (Scheme 5). When the loading of benzylamine was reduced to 1.2 equiv, product **6a**, which was formed from the C-C bond formation at the γ-position of the allyl ketone, was obtained as the major product in 65%, and α-adduct **5a** was obtained in 15% (Scheme 5). With the use of 1.2 equiv of benzylamine, various Mannich products **6** were obtained as the major products from the bond formation at the γ-position of the allyl ketones (Scheme 6). Note that Mannich reactions at the γ-position of the allyl ketones have not been readily achieved previously.[8c]

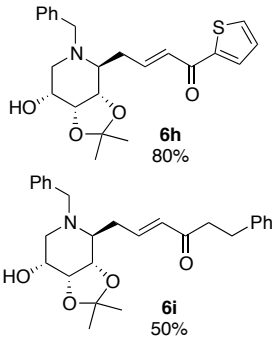
Scheme 5. Mannich reactions of **1a** with allyl phenyl ketone.



Scheme 6. Mannich reactions of **1a** with allyl ketones to afford **6**.[a]

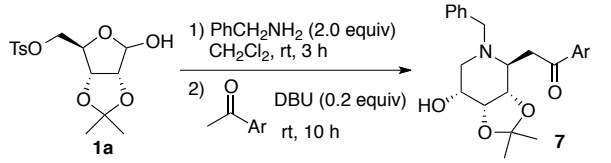


6	Ar	yield
6b	C_6H_4-4-OMe	80%
6c	1-naphthyl	76%
6d	C_6H_4-4-Cl	70%
6e	C_6H_4-4-F	68%
6f	C_6H_3-4-F-2-Me	66%
6g	C_6H_4-4-Me	72%



[a] Conditions: **1a** (1.0 mmol, 1.0 equiv) and $PhCH_2NH_2$ (1.2 equiv) in CH_2Cl_2 (5.0 mL) at rt (25 °C) for 3 h; then allyl ketone (1.2 equiv). Products **6** were isolated as single diastereomers.

Scheme 7. Mannich reactions of **1a** with aryl methyl ketones to afford **7**.[a]



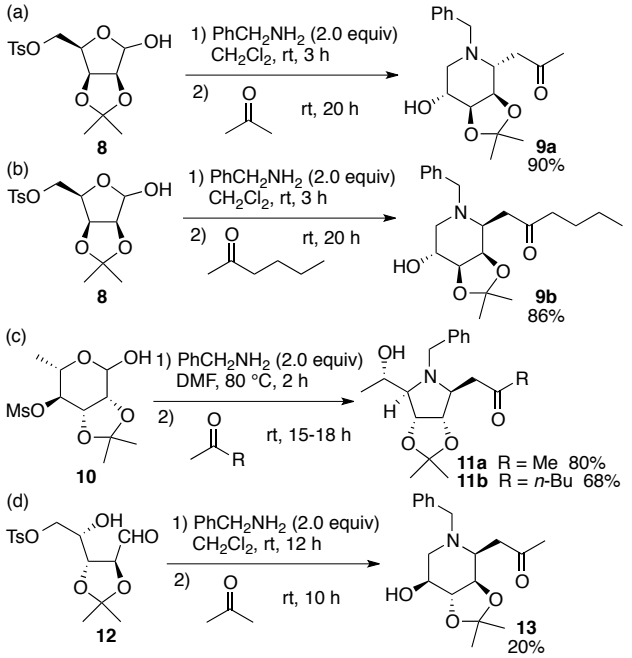
7	Ar	yield
7a	Ph	90%
7b	2-naphthyl	86%
7c	C_6H_4-4-Me	84%
7d	C_6H_4-4-Br	80%

[a] Conditions: **1a** (0.45 mmol, 1.0 equiv) and $PhCH_2NH_2$ (2.0 equiv) in CH_2Cl_2 (2.0 mL) at rt (25 °C) for 3 h; then addition of aryl methyl ketone (1.5 equiv) and DBU (0.2 equiv). Products **7** were isolated as single diastereomers.

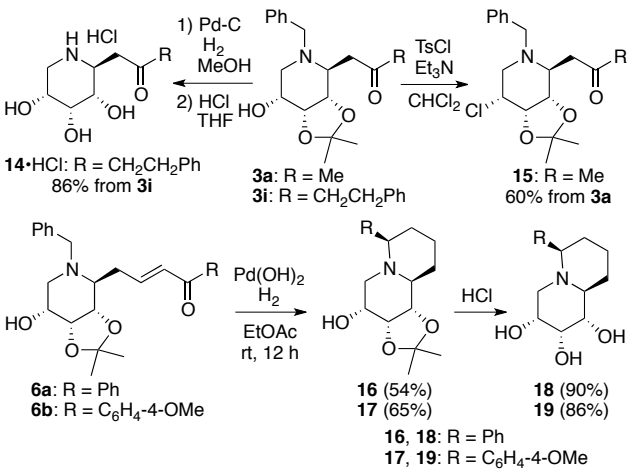
For the reaction of **1a** with acetophenone derivatives, the use of DBU[9] (0.2 equiv) as additive at the ketone reaction step led to the formation of Mannich products **7** (Scheme 7).

The Mannich reaction strategy to afford piperidine derivatives was further evaluated in the reactions of various sugar derivatives (Scheme 8). From the reactions of D-lyxose derivative **8**,[10] piperidine derivatives **9** were obtained (Scheme 8a, b). For product **9b**, the isomer obtained had the *syn* configuration between the formed C-C bond and the hydroxy group at the originally 2-position of lyxose when initially isolated. The dr became 1:1 when **9b** was stored at rt (25 °C). These results suggest that product stereochemistry observed is the result of the steric effects during the C-C bond formation and is influenced by the thermodynamic stability of the product (see Supporting Information). From L-rhamnose derivative **10**,[11] pyrrolidine derivatives **11** were also synthesized (Scheme 8c). In these reactions, the iminium ion formation step was heated to 80 °C, but reaction with the ketone was performed at rt (25 °C). From **12**, which had acetonide protection of the *trans*-hydroxy groups, piperidine derivative **13** was obtained, although the yield was moderate (Scheme 8d, not optimized).

Scheme 8. Mannich reactions of various sugar derivatives.



Scheme 9. Transformations of the Mannich products.



The utility of the Mannich reaction methods was demonstrated by transformations of the products (Scheme 9). Deprotection of the benzyl and the acetonide groups of **3i** afforded **14**. Chloride derivative **15** was obtained from **3a** by treating with tosyl chloride in the presence of Et_3N through the retention of the stereochemistry of the hydroxy group of **3a**. Mannich reaction products **6a** and **6b** were transformed to quinolizine derivatives[1f,4c,11] **16** and **17**, respectively in one pot. After deprotection of the acetonide group, polyhydroxy-functionalized quinolizines **18** and **19** were obtained.

In summary, we have developed Mannich reactions of sugar derivatives with ketones to afford polyoxy-functionalized piperidine derivatives. The conditions leading to the formation of piperidine derivatives rather than tetrahydrofuran derivatives were identified. Further, with the use of developed Mannich reactions, polyhydroxy-functionalized bicyclic piperidine derivatives were readily accessed.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional discussion, experimental procedures, characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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