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Base-promoted reaction of methyl 4,6-*O*-benzylidene-3-deoxy-hexopyranosid-2-ulose and various arylamines

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ABSTRACT

Reaction of methyl 4,6-*O*-benzylidene-3(2)-deoxy-hexopyranosid-2(3)-ulose (**1**) with various arylamines under Bargellini reaction conditions was investigated. A series of unique enaminoketones **3–12** was obtained unexpectedly under basic conditions in 52–72% yield.

3-Amino-prop-2-en-1-ones are a class of unique compounds bearing a double bond in *Z*-conformation due to the intramolecular H-bonding between the carbonyl and the NH group. These compounds are generally prepared by transition-metal-catalyzed transformation of propargyl alcohol with an appropriate amine.[1,2] During our study on the glycosidation of glycals and arylamines,[3,4] we proposed to synthesize α–aminoacid **2** by treating methyl 4,6-*O*-benzylidene-3(2)-deoxy-α-D-*erythro*-hexopyranosid-2(3)-ulose (**1**) with 4-methoxyaniline under Bargellini reaction conditions.[5–8] The mechanism of this type of reactions includes deprotonation of chloroform by NaOH followed by nucleophilic attack on the ketone **1**[9] to yield dichloro epoxide intermediate **I**. Subsequent regioselective epoxide ring-opening by aniline followed by hydrolysis of the resulting acid chloride **II** (Fig. 1) would yield the expected product **2**.

To our surprise, the reaction of pyranose **1** with 4-methoxyaniline and NaOH in $CHCl_3$ under standard Bargellini reaction conditions went through smoothly, but the product we obtained was not the expected compound **2**, instead (*Z*)-1-(2-phenyl-6*H*-1,3-dioxin-4-yl)-3-(4-methoxyphenylamino) prop-2-en-1-one (**3**) was formed in 52% isolated yield.

Enaminoketone **3** was characterized by spectroscopic data (^1H and ^{13}C NMR, MS, HRMS, HMQC, ^1H–13C COSY). Such unusual structure of **3** was also evidenced by the HMBC correlations between H-5′ (δ_H 5.84 ppm) and C-1 carbonyl (δ_C 183.8 ppm), H-3 (δ_H 7.36 ppm) and C-1 carbonyl, as well as H-3 and the quaternary C-5 in the aniline phenyl moiety (Fig. 2). The *Z*-conformation of the double bond in **3** was ascertained by the coupling constant[1] of 7.8 Hz between the two vinyl protons. The chemical shift of NH moved to much downfield (δ_H 12.13 ppm) indicating the existence of an intramolecular H-bonding with the carbonyl group. Finally, single X-ray crystal of enaminoketone **3** was obtained after a careful crystallization from $CHCl_3$ that further secured the unique structure of the product (Fig. 2).

To achieve a better yield, the reaction condition was optimized. Originally, the reaction was conducted under typical Bargellini reaction condition in which 1.0 equiv of 4-methoxyaniline was reacted with 3.0 equiv of ketone **1**, 5.0 equiv of $CHCl_3$, and NaOH in THF. Compound **3** was obtained in 52% isolated yield (entry 1, Table 1). Reducing the amount of NaOH to 3.0 equiv improved the work-up of the reaction and slightly improved the yield (entry 2). It is of note that compound **3** was obtained in identical yield with or without the addition of $CHCl_3$ confirming that the originally proposed Bargellini reaction process did not occur. Decreasing NaOH to 1.0 equiv (entry 3) or reducing the amount of ketone **1** (entry 4) significantly slowed down the reaction process. Increasing the amount of ketone **1** to 5.0 equiv did not change the yield significantly and compound **3** was isolated in 55% yield (entry 5). It was further found that LiOH was also able to promote the reaction leading to product **3** in 56% yield (entry 6), compatible to that using NaOH as the base. Weaker base Cs_2CO_3 initiated the reaction as well but gave a much lower yield (entry 7). However, the reaction did not occur using other organic or inorganic bases

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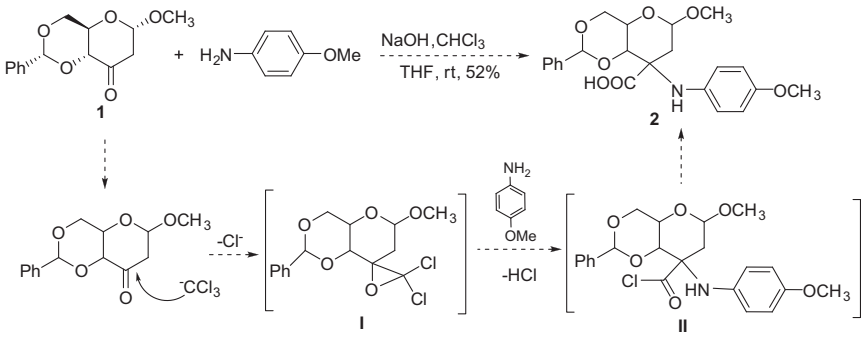


Figure 1. Proposed reaction of pyranose **1** with 4-methoxyaniline under Bargellini reaction condition.

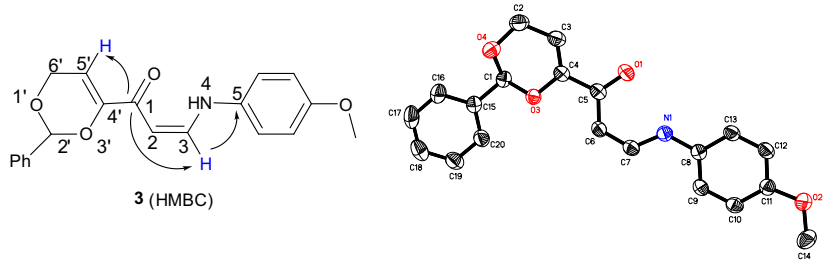
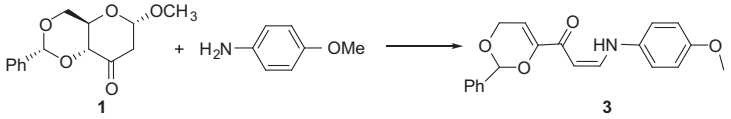


Figure 2. HMBC and X-ray crystal analyses of **3**.

Table 1
Optimization of reaction conditions[a]



Entry	Base/acid	Equiv	Ratio (ketone 1:4-methoxyaniline)	Yield[b] (%)
1	NaOH	5	3:1	52
2	NaOH	3	3:1	58
3	NaOH	1	3:1	Trace
4	NaOH	3	1:1	<20
5	NaOH	3	5:1	55
6	LiOH	3	3:1	56
7	Cs_2CO_3	3	3:1	23
8	Na_2CO_3	3	3:1	Trace
9	DBU	3	3:1	NR[c]
10	EtN(^{i}Pr)$_2$	3	3:1	NR[c]
11	NEt_3	3	3:1	NR[c]
12	$BF_3{\cdot}Et_2O$	3	3:1	NR[c]
13	$FeCl_3$	3	3:1	NR[c]
14	$TiCl_4$	3	3:1	NR[c]

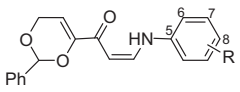
[a] The reaction was conducted with 1.0 equiv of 4-methoxyaniline, appropriate amount of ketone **1**, 5.0 equiv of chloroform, and appropriate amount of NaOH in 10 mL of anhydrous THF at rt overnight.
[b] Isolated yield.
[c] NR = no reaction.

(Na_2CO_3, DBU, NEt_3, EtN(^{i}Pr)$_2$ (entries 8–11). In addition, several Lewis acids were also used and no reaction was observed at all (entries 12–14).

Based on the results obtained above, the optimal reaction condition is to use 3.0 equiv of ketone **1**, 1.0 equiv of aniline, and 3.0 equiv of NaOH in THF leading to product **3** in 58%. To explore the practicality of this reaction in the preparation of enaminoketones, various arylamines were used to react with ketone **1**, and the results were summarized in Table 2.[10] Most arylamines participated in this reaction and the corresponding enaminoketones **3**–**12** were obtained in 52–72% yields. Both mono- and di-substituted arylamines gave compatible yields. Reactions using arylamines bearing larger substituent (entry 8), or *ortho*-substituent (entry 6) also led to good yields. Arylamines with an electron-withdrawing substituent (entry 10) participated in this reaction as well and the corresponding product **12** was obtained in 52% yield. However, reaction using *N*-methyl substituted arylamine did not go through apparently due to the steric effect of the *N*-methyl group (entry 11). Further, using alkyl amines also did not afford the expected products.

To rationale this reaction, a tentative base-initiated mechanism was proposed. As described in Figure 3, ketone **1** would easily lose a proton (α to the carbonyl) upon a base-attacking to form an anion intermediate **I**. Ring-opening would then occur to form

Table 2
Reactions of ketone **1** with various arylamines[a]

Entry	Arylamine		Yield[b] (%)
1	4-MeO-PhNH$_2$	**3** (R = 8-MeO)	58
2	Aniline	**4** (R = H)	54
3	*p*-Toluidine	**5** (R = 8-Me)	69
4	4-Et-PhNH$_2$	**6** (R = 8-Et)	71
5	4-EtO-PhNH$_2$	**7** (R = 8-EtO)	63
6	2-MeO-PhNH$_2$	**8** (R = 6-MeO)	55
7	*m*-Toluidine	**9** (R = 7-Me)	63
8	4-Mor-PhNH$_2$	**10** (R = 8-Mor[c])	65
9	3,4-Di-MeO-PhNH$_2$	**11** (R = 7,8-di-MeO)	72
10	4-Br-PhNH$_2$	**12** (R = 8-Br)	52
11	*N*-Me-PhNH$_2$	—	—[d]

[a] The reaction was conducted on 1.0 mmol scale of arylamine using the optimized conditions.
[b] Isolated yield.
[c] Mor = morpholin-4-yl.
[d] No reaction.

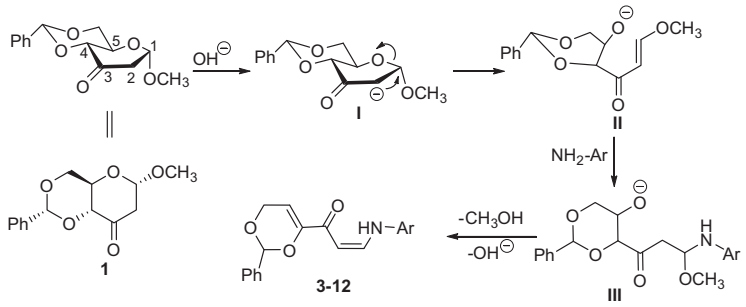


Figure 3. Possible base-initiated mechanism.

enolate-like **II**. Subsequent Michael addition of arylamine generated species **III** that then underwent elimination of MeOH and OH^- under basic condition to yield products **3–12**. Theoretically, this reaction also likely went through by a Lewis acid, however, replacing NaOH with Lewis acids such as BF_3, $TiCl_4$, or $FeCl_3$ did not promote this reaction at all (Table 1, entries 12–14).[11]

In summary, reaction of methyl 4,6-*O*-benzylidene-3(2)-deoxyhexopyranosid-2(3)-ulose (**1**) with various arylamines under Bargellini reaction conditions was investigated. A series of unique enaminoketones **3–12** was obtained in 52–72% yield, and a base-promoted mechanism was proposed.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.106.

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10. General experimental procedure: To a solution of methyl 4,6-*O*–benzylidene-2-deoxy-α-D-erythro-hexopyran-osid-3-ulose (129 mg, 0.49 mmol) and arylamines (0.16 mmol) in THF (10 mL) NaOH (20 mg, 0.48 mmol) were added. The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 12 h. The solution was extracted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give a residue which was then purified by chromatography on silica gel to afford products **3**–**12** as yellow solid.
*For (Z)-3-(4-methoxyphenylamino)-1-(2-phenyl- 4H-1,3-dioxin-6-yl) prop-2-en-1-one (**3**)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (d, J = 12.4 Hz, 1H, NH), 7.59 (m, 2H, Ar), 7.41 (m, 3H, Ar), 7.40 (m, 1H, H-3′), 7.02 (d, J = 9.2 Hz, 2H, ArOMe), 6.88 (d, J = 9.2 Hz, 2H, ArOMe), 6.12 (d, J = 1.6 Hz, 1H, H-2′), 5.84 (d, J = 7.6 Hz, 1H, H-2), 5.83 (s, 1H, H-5′), 4.70 (dd, J = 17.2, 2.4 Hz, 1H), 4.57 (dd, J = 17.2, 3.6 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 156.6, 151.0, 146.8, 136.9, 133.4, 129.3, 128.4 (2C), 126.4 (2C), 118.1 (2C), 114.9 (2C), 105.5, 98.3, 91.50, 65.1, 55.6; MS (EI-LR) 337 (M+); HRMS (EI) calcd for $C_{20}H_{19}NO_4$ (M+) 337.1314; found 337.1295. *For (Z)-1-(2-phenyl-4H-1,3-dioxin-6-yl)-3-(phenylamino) prop-2-en-1-one (**4**)*: 54%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.04 (d, J = 11.7 Hz, 1H), 7.58 (dd, J = 6.6, 2.7 Hz, 2H), 7.44 (m, 4H), 7.33 (t, J = 7.8 Hz, 2H), 7.08 (t, J = 7.8 Hz, 3H), 6.13 (m, 1H), 5.88 (d, J = 7.8 Hz, 1H), 5.82 (s, 1H), 4.69 (dd, J = 17.5, 2.1 Hz, 1H), 4.56 (dd, J = 17.4, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 150.9, 145.9, 139.8, 136.9, 129.7(2C), 129.3, 128.4(2C), 126.4(2C), 124.0, 116.4(2C), 105.8, 98.3, 92.3, 65.0; MS (EI-LR) 307 (M^+); HRMS (EI) calcd for $C_{19}H_{17}NO_3$ (M^+) 307.1208; found 307.1190. For *(Z)-1-(2-phenyl-4H-1,3-dioxin-6 yl)-3-(p-tolyl amino)prop-2-en-1-one (**5**)*: 69%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.06 (d, J = 12.9 Hz, 1H), 7.58 (dd, J = 7.5, 2.1 Hz, 2H), 7.45 (m, 4H), 7.13 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.12 (dd, J = 3.6, 2.4 Hz, 1H), 5.87 (d, J = 7.8 Hz, 1H), 5.82 (s, 1H), 4.69 (dd, J = 17.4, 2.2 Hz, 1H), 4.56 (dd, J = 17.4, 3.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 184.0, 150.9, 146.3, 137.5, 133.8, 130.2(2C), 129.3, 128.4(2C), 126.4(2C), 116.5(2C), 105.6, 98.3, 96.6, 91.8, 60.5, 20.8; MS (EI-LR) 321 (M^+); HRMS (EI) calcd for $C_{20}H_{19}NO_3$ (M^+) 321.1365; found 321.1366.

11. In the course of submission of this Letter, one reviewer suggested an alternative mechanism (showing below), where base-attack and deprotonation occur at the C-4, instead of C-2. Although C-2 is generally more active than the C-4 in substrate **1** due to the effect of the C-1 acetal, this mechanism can not be excluded.