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Direct addition of 2-methylazines to aryl glyoxals for the synthesis of α-hydroxy ketones

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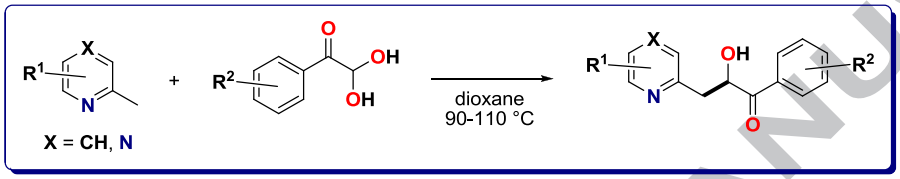


ABSTRACT. A catalyst-free protocol for the reaction of 2-methylazines and aryl glyoxal hydrates leading to α-hydroxy ketones bearing azaarene moiety is described. The process is operationally simple and can be applied to a broad range of substrates.

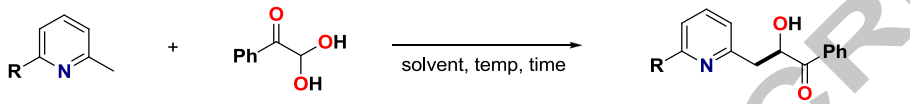
Keywords: 2-methylazines, aryl glyoxals, α-hydroxyketones, azaarenes

Modern organic synthesis strives for development of novel, sustainable and operationally simple procedures. Many of recent efforts have been focused on the direct functionalization of ubiquitous C(sp^3)–H bond.[1] In this regard, the additions of 2-methylazines to carbonyl[2] or imine[3] groups as well as to other electrophiles[4] have recently emerged as an efficient and atom economic strategy to access various types of azaarene containing building blocks. Typically, such transformations utilize catalytic amounts of Lewis or Brønsted acid while some of very recent approaches are catalyst-free.[5] Following the success of these procedures, we have developed a direct catalyst-free coupling of 2-methylazines **1** and aryl glyoxal hydrates **2**[6,7] for the straightforward synthesis of a wide range of α-hydroxyketones **3** bearing azaarene moiety. Herein we present the scope and limitations of this process.

We started our investigation with a search for the optimal reaction parameters (Table 1). We chose additions of 2-picoline (**1a**) and 2,6-lutidine (**1b**) to phenyl glyoxal hydrate (**2a**) as two model reactions. Initially, we have found that **2a** reacts with **1a** (1.2 equiv.) at 110 °C in dioxane delivering α-hydroxyketone **3a** in 21 % NMR yield which corresponds to 17 % isolated yield after column chromatography (Table 1, entry 1). Increasing the access of **1a** up to 3 equiv. resulted in enhancement of NMR and isolated yields of **3a** up to 49 % and 44 % respectively (Table 1, entry 2). Further variations in solvent, dilution, reagents ratio as well as

in reaction time and temperature did not provide an additional improvement (Table 1, entries 3-14). The reaction of phenyl glyoxal hydrate (**2a**) with 2,6-lutidine (**1b**) that contain two reactive methyl groups (Table 1, entries 15-18) required only 2 equiv. of **1b** to achieve a reasonable yield of α-hydroxyketone **3b** (Table 1, entry 17).

Table 1. Optimization of reaction parameters[a]



1 x equiv. **2a** **3**

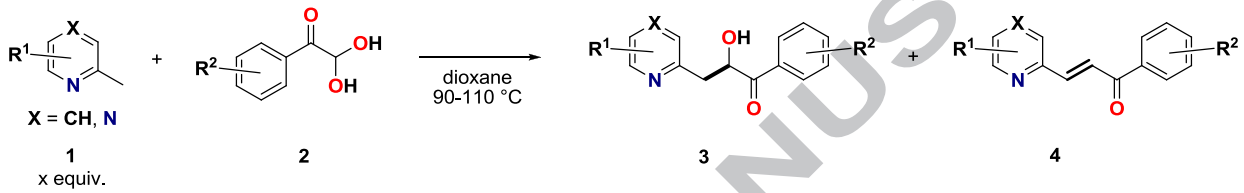
Entry	R (**1**)	x	Solvent	Dilution, M[b]	Temp, °C[c]	Time, h	Product (**3**)	Yield[d]
1	H (**1a**)	1.2	dioxane	0.5	110	20	**3a**	21 (17)[e]
2	**H (1a)**	**3**	**dioxane**	**0.5 M**	**110**	**14**	**3a**	**49 (44)[e]**
3	H (**1a**)	3	toluene	0.5 M	110	14	**3a**	24
4	H (**1a**)	2	dioxane	2	110	25	**3a**	22
5	H (**1a**)	2	dioxane	2	110	14	**3a**	25
6	H (**1a**)	2	toluene	2	110	14	**3a**	12
7	H (**1a**)	3	dioxane	0.67 M	110	14	**3a**	45
8	H (**1a**)	3	dioxane	0.5 M	110	20	**3a**	47
9	H (**1a**)	3	dioxane	0.33 M	110	14	**3a**	41
10	H (**1a**)	5	dioxane	0.33 M	110	14	**3a**	41
11	H (**1a**)	3	dioxane	0.2 M	110	20	**3a**	36
12	H (**1a**)	2	dioxane	0.5 M	110	14	**3a**	41
13	H (**1a**)	3	dioxane	0.5 M	140	14	**3a**	32
14	H (**1a**)	3	dioxane	0.5 M	90	20	**3a**	13
15	Me (**1b**)	3	dioxane	0.33 M	110	14	**3b**	62
16	Me (**1b**)	3	dioxane	0.5 M	110	14	**3b**	63
17	**Me (1b)**	**2**	**dioxane**	**0.5 M**	**110**	**14**	**3b**	**63 (62)[e]**
18	Me (**1b**)	1.5	dioxane	0.5 M	110	14	**3b**	48

[a] The reactions were run on 1 mmol scale. [b] Based on **2a**. [c] This refers to the oil bath temperature. [d] Yields are determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [e] Isolated yield is given in parentheses.

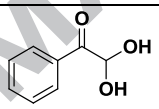
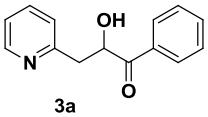
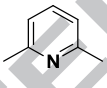
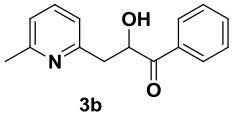
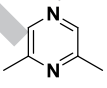
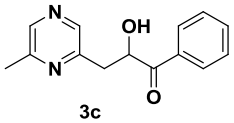
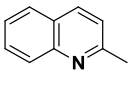
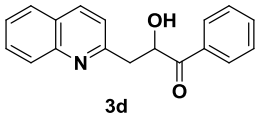
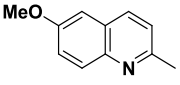
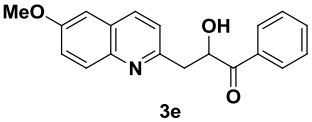
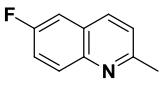
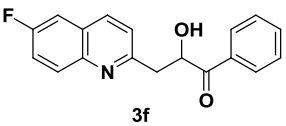
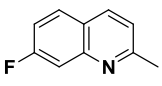
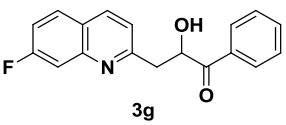
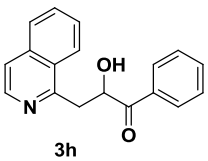
Having these results in hand, we moved to the substrate scope evaluation (Table 2).[8] At first, we studied additions of various 2-methylazines **1a-h** to phenyl glyoxal hydrate (**2a**) (Table 2, entries 1-8). 2,6-Lutidine (**1b**) showed a better performance compared to 2-picoline (**1a**) which could be ascribed to the presence of two reactive methyl groups (Table 2, entry 2 versus entry 1). In contrast, 2,6-dimethylpyrazine (**1c**) delivered α-hydroxyketone product **3c** in only poor yield of 12 % (Table 2, entry 3). 2-Methylquinolines **1d-g** and 1-methylisoquinoline **1h** reacted well delivering desired α-hydroxyketones **3d-h** with the yields ranging from 37 to 55 % (Table 2, entries 4-8). For the reactions with substrates **1d** and **1h**, chalcone-type side products **4d** and **4h** were isolated in addition to the standard α-hydroxyketone products **3d** and **3h** (Table 2, entries 4 and 8). Next, we turned our attention to the reactions of various aryl glyoxal hydrates **2b-d** in combination with 2-methylazines **1a,b,d,e**. All reactions were successful allowing to obtain diverse α-hydroxyketones **3i-q**

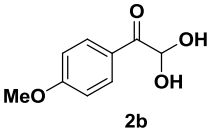
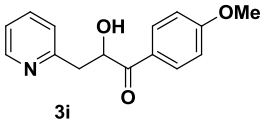
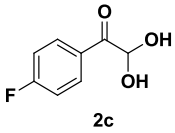
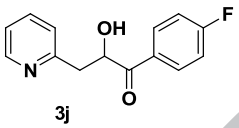
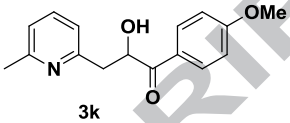
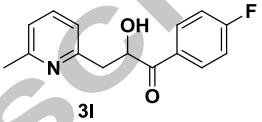
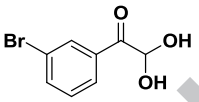
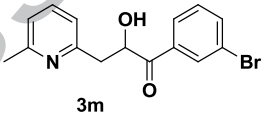
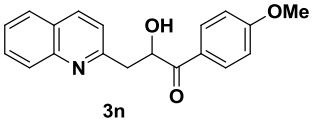
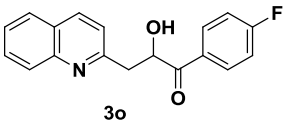
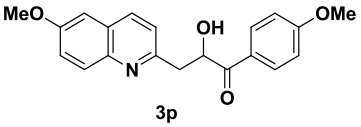
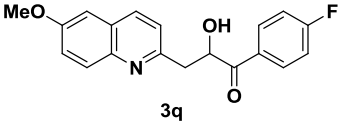
in 31 to 65 % yield (Table 2, entries 9-18). It is important to stress that some of the reactions required higher dilution and the use of reduced temperature of either 95 °C or 100 °C in order to avoid the formation of minor quantities of **5**-type side product resulting from the double addition of 2-methylazine **1** to aryl glyoxal hydrate **2**. Such side product, if formed, could not be separated from the corresponding desired product **3** by the column chromatography and, thus, hampers its isolation in pure form. However, in one case namely for the reaction of 4-chloro-2-methylquinoline (**1i**) with phenyl glyoxal hydrate (**2a**) the double addition product **5** was obtained as a major product and no α-hydroxyketone **3r** was formed (Scheme 1).

Table 2. Scope of the process[a]

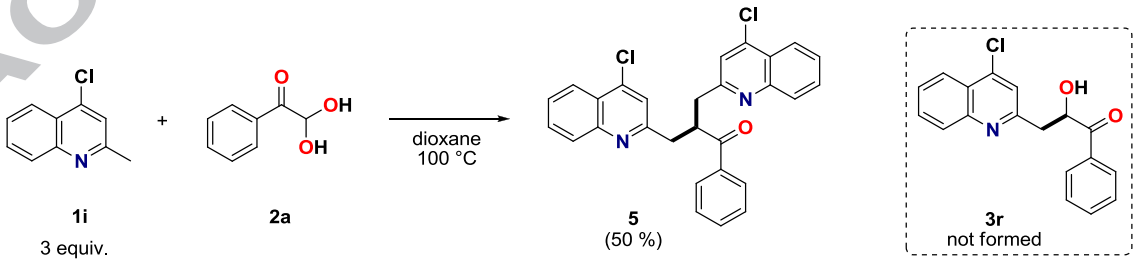


1 x equiv. **2** **3** **4**

Entry	x	Temp, °C[b]	Dilution, M[c]	**1**	**2**	Product (**3**)	Yield[d]
1	3	110	0.5	 **1a**	 **2a**	 **3a**	44
2	2	110	0.5	 **1b**	**2a**	 **3b**	62
3	3	110	0.5	 **1c**	**2a**	 **3c**	12
4	3	100	0.33	 **1d**	**2a**	 **3d**	55 (20)[e]
5	3	110	0.5	 **1e**	**2a**	 **3e**	46
6	3	110	0.33	 **1f**	**2a**	 **3f**	47
7	3	100	0.33	 **1g**	**2a**	 **3g**	51
8	3	95	0.33	 **1h**	**2a**	 **3h**	37 (17)[e]

9	3	110	0.5	**1a**	 **2b**	 **3i**	31
10	3	110	0.5	**1a**	 **2c**	 **3j**	46
11	2	110	0.5	**1b**	**2b**	 **3k**	58
12	2	110	0.5	**1b**	**2c**	 **3l**	52
13	2	110	0.5	**1b**	 **2d**	 **3m**	35
14[f]	4						38
15	3	100	0.33	**1d**	**2b**	 **3n**	58
16	3	100	0.33	**1d**	**2c**	 **3o**	50
17[g]	3	110	0.25	**1e**	**2b**	 **3p**	65
18[h]	3	110	0.5	**1e**	**2c**	 **3q**	54

[a] Unless otherwise stated all reactions were run on 1 mmol scale for 14 h. [b] This refers to the oil bath temperature. [c] Based on **2**. [d] Isolated yields. [e] The yield of side product **4** is given in parentheses. [f] The reaction was run for 20 h. [g] The reaction was run on 0.5 mmol scale. [h] The reaction was run on 0.6 mmol scale.



Scheme 1. Double addition of 4-chloro-2-methylquinoline (**1i**) to phenyl glyoxal hydrate (**2a**)

The obtained products **3a-q**, **4d,h** and **5** were characterized using ^{1}H and ^{13}C NMR spectroscopy and HRMS. In addition, the structures of α-hydroxyketone **3l** and the double addition product **5** were assured by X-ray crystallographic analysis.[9]

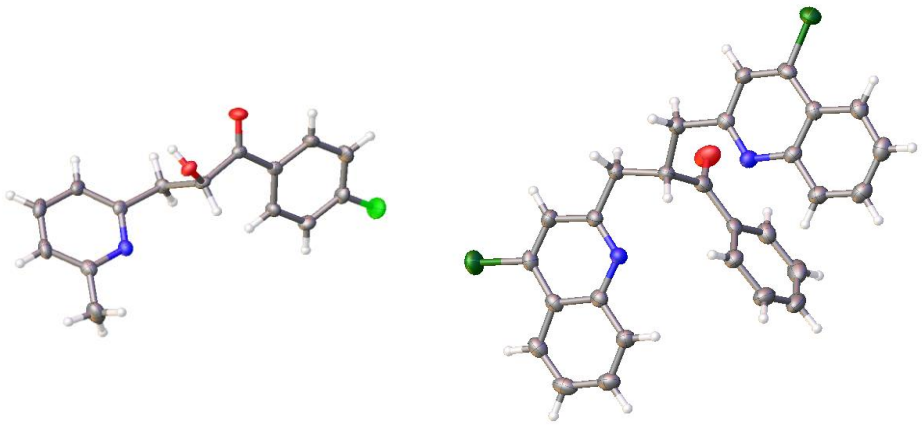


Figure 1. X-ray crystallographic structures of compounds **3l** and **5**.

In conclusion, we have demonstrated that the aryl glyoxal hydrates could be successfully used as an electrophilic carbonyl component in the reactions with 2-methylazine nucleophiles. The developed catalyst-free protocol allowed to prepare a small library of azaarene containing α-hydroxyketones in moderate yields.

Acknowledgements

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Supplementary data

Full experimental procedures as well as copies of ^{1}H and ^{13}C NMR spectra of the compounds associated with this article can be found, in the online version, at http://dx.doi.org/.

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6 A previous attempt by Zhou, Uozumi and coworkers to react phenyl glyoxal (**2a**) with quinaldine (**1d**) in the presence of $Fe(OAc)_2$ (10 mol%) met with failure due to decomposition of **2a** (see ref. [2b]).

7. For a focused review about the application of aryl glyoxals in heterocyclic chemistry, see: Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958−3043.

8. *Representative procedure for additions of 2-methylazines **1** to aryl glyoxal hydrates **2** exemplified by the synthesis of 2-hydroxy-1-phenyl-3-(pyridin-2-yl)propan-1-one (**3a**).* Phenyl glyoxal hydrate (**2a**) (152 mg, 1 mmol) was placed into screw cap vial and dissolved in dioxane (2 ml) followed by addition of 2-picoline (**1a**) (279 mg, 3 mmol). The reaction mixture was sealed and kept under stirring at 110 °C for 14 h. The resulting mixture was diluted with DCM and evaporated with silica gel. Column chromatography with heptane-EtOAc (20→50 %) delivered pure **3a** (100 mg, 44 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59-8.49 (m, 1H), 8.11-8.01 (m, 2H), 7.66-7.56 (m, 2H), 7.55-7.44 (m, 2H), 7.23-7.11 (m, 2H), 5.55 (dd, J = 3.3, 8.5 Hz, 1H), 4.64 (bs, 1H), 3.36 (dd, J = 3.3, 14.5 Hz, 1H), 3.01 (dd, J = 8.5, 14.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 158.1, 149.3,

136.7, 134.2, 133.9, 129.1, 128.9, 124.4, 121.9, 73.5, 43.0; HRMS (ESI, $[M+H]^+$) for $C_{14}H_{14}NO_2$ calcd. 228.1019, found 228.1025.

9. CCDC 1406639 and 1406640 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html