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Iodine-Mediated One-Pot Synthesis of 2-(Piperazin-1-yl)pyrazine Derivatives from *N*-Alkyl Piperazines

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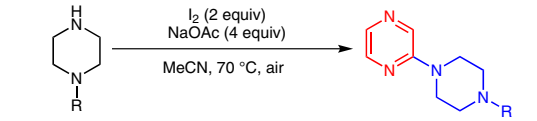

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Abstract An iodine-mediated one-pot reaction of *N*-alkyl piperazines is described for the first time. This transformation provides a straightforward and facile pathway to the synthesis of 2-(piperazin-1-yl)pyrazine derivatives with the corresponding *N*-alkyl piperazines as single material. Based on a series of control experiments, a plausible reaction mechanism has been proposed.

Key words iodine, sodium acetate, one-pot reaction, 2-(piperazin-1-yl)pyrazine, *N*-alkyl piperazine

Of the more than 20 million chemical compounds currently registered, about one half contain heterocyclic systems.[1] Among them, 2-(piperazin-1-yl)pyrazines is a vital class of heterocyclic compounds synthesized in the laboratory.[2,3] Also, 2-(piperazin-1-yl)pyrazines are important units in many molecules possessing biological activity.[4–6] The presence of this structural motif in many substances of biological significance have led to many approaches being developed to access this chemotype, many of which have been employed in the preparation of pharmaceutical agents.[5–7]

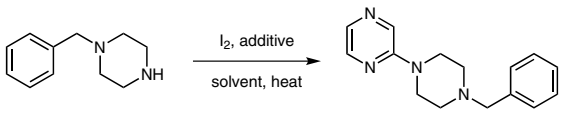
Molecular iodine, firstly produced from brine in Japan, has been used in organic synthesis for a long time.[1,8] In recent years, molecular iodine has received considerable attention as an inexpensive, nonmetallic, nontoxic, environmentally benign and readily available reagent for various organic transformations under mild and convenient conditions to afford the corresponding products.[9–12] Herein, we would like to disclose an efficient and practical synthesis of 2-(piperazin-1-yl)pyrazines by I_2-mediated one-pot reaction of N-substituted piperazines in acetonitrile.

According to the reported literature,[13–15] I_2/NaOAc is an efficient reagent system for N-demethylation of tertiary amines. During the course of our attempt to a systematic investigation of N-dealkylation of tertiary amines, we investigated the reaction of 1-benzylpiperazine (10 mmol) with I_2 (1.5 equiv) and NaOAc (3.0 equiv) in methanol (20 mL). After refluxing for four hours, two major components including the starting material (**1a**) were detected by analytical TLC. The other major component was then purified by column chromatography on basic alumina. Surprisingly, this compound was identified as 2-(4-benzylpiperazin-1-yl)pyrazine (**2a**) by spectroscopic methods including 1D and 2D NMR and HRMS analysis.

Encouraged by the above results, 1-benzylpiperazine (**1a**) was chosen as the model substrate to optimize reaction conditions including the amount of I_2, solvents, reaction temperatures, reaction times, and different additives under ambient air conditions. The results are summarized in Table 1. As listed, when the model reaction was carried out in the presence of different amount of I_2 in methanol at 80 °C for four hours, 2.0 equivalent of I_2 exhibited enough reactivity with 71% yield of the desired product **2a** (Scheme 1 and Table 1, entry 2). When the model reaction was performed in different solvents including acetonitrile, ethanol, CH_2Cl_2, DCE, THF, DMF, 1,4-dioxane and H_2O (Table 1, entries 3–11), 21–88% yields of product **2a** were obtained, representing the results that acetonitrile was the best solvent choice. Subsequently, the influence of reaction temperature was investigated. The results revealed that when

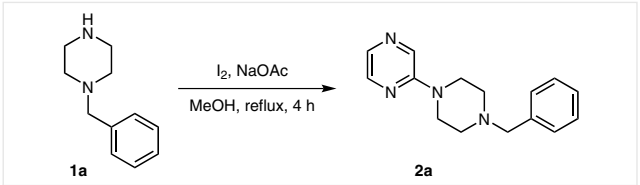
the temperature was raised to 70 °C, the yield of the desired product **2a** increased to 88% (Table 1, entry 13), as well as lower and further higher temperature could not make it better. Furthermore, various commercially available bases (Table 1, entries 17–21) were also tested in the presence of I_2 (2.0 equiv), however, the outcomes were not encouraging. Additionally, treatment of **1a** with I_2 (2 equiv) alone induced a lower yield, whereas NaOAc alone could not induce the reaction even after 24 hours (Table 1, entry 23). These results suggested that a weakly alkaline environment might be conducive to the reaction. On basis of these results, the optimized reaction conditions were determined as the substrate (10 mmol), I_2 (2 equiv) and NaOAc (4 equiv) in MeCN (20 mL) at 70 °C under air.

Table 1 Conditions Optimization for the Synthesis of **2a**[a]



Entry	I_2 (equiv)	Solvent	Additive (equiv)	Time (h)	Temp (°C)	Yield (%)[b]
1	1.5	MeOH	NaOAc (2.0)	4	80	59
2	2.0	MeOH	NaOAc (3.0)	4	80	71
3	2.5	MeOH	NaOAc (4.0)	4	80	65
4	2.0	MeCN	NaOAc (4.0)	4	80	88
5	2.0	EtOH	NaOAc (4.0)	4	80	50
6	2.0	CH_2Cl_2	NaOAc (4.0)	4	80	36
7	2.0	DCE	NaOAc (4.0)	4	80	43
8	2.0	THF	NaOAc (4.0)	4	80	32
9	2.0	DMF	NaOAc (4.0)	4	80	23
10	2.0	1,4-dioxane	NaOAc (4.0)	4	80	52
11	2.0	H_2O	NaOAc (4.0)	4	80	21
12	2.0	MeCN	NaOAc (4.0)	4	60	72
13	2.0	MeCN	NaOAc (4.0)	4	70	88
14	2.0	MeCN	NaOAc (4.0)	4	90	79
15	2.0	MeCN	NaOAc (4.0)	2	70	89
16	2.0	MeCN	NaOAc (4.0)	1	70	66
17	2.0	MeCN	KOAc (4.0)	2	70	88
18	2.0	MeCN	$NaHCO_3$ (4.0)	2	70	81
19	2.0	MeCN	Na_2CO_3 (4.0)	2	70	72
20	2.0	MeCN	K_2CO_3 (4.0)	2	70	56
21	2.0	MeCN	NaOH (4.0)	2	70	0
22	2.0	MeCN	–	24	70	66
23	0	MeCN	NaOAc (4.0)	24	70	0

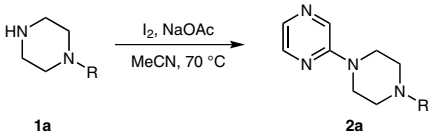
[a] Reaction conditions: **1a** (10 mmol), solvent (20 mL) in the presence of I_2, heated for the corresponding time.
[b] Isolated yield.



Scheme 1 The reaction of **1a** with I_2 and NaOAc

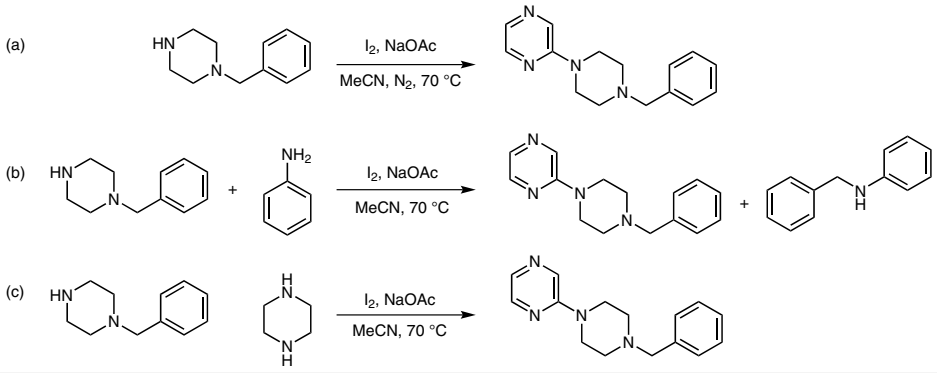
After establishing the optimized reaction conditions, we next investigated the scope and limitations of this protocol. As shown in Table 2, a variety of piperazines bearing different alkyl groups reacted smoothly affording the corresponding 2-(piperazin-1-yl)pyrazines **2a–q** in moderate to good yields. In order to further expand the scope of this methodology, we next applied this process to 1-phenylpiperazine (**1r**) and 1-benzoylpiperazine (**1s**). Unfortunately, the reaction with 1-phenylpiperazine (**1r**) and 1-benzoylpiperazine (**1s**) failed to produce the desired products.

Table 2 I_2-Mediated Reaction of Piperazines[a]



Entry	R	Substrate	Product	Yield (%)[b]
1	benzyl	**1a**	**2a**	89
2	methyl	**1b**	**2b**	85
3	ethyl	**1c**	**2c**	85
4	hydroxyethyl	**1d**	**2d**	83
5	2-methoxyethyl	**1e**	**2e**	86
6	1-hydroxyethoxyethyl	**1f**	**2f**	88
7	isopropyl	**1g**	**2g**	81
8	cyclohexanyl	**1h**	**2h**	89
9	cyclohexylmethyl	**1i**	**2i**	86
10	(4-*tert*-butylphenyl)methyl	**1j**	**2j**	83
11	1,3-benzodioxol-5-ylmethyl	**1k**	**2k**	89
12	2,3,4-trimethoxybenzyl	**1l**	**2l**	82
13	2,2-bisphenylethyl	**1m**	**2m**	81
14	3-pyridylmethyl	**1n**	**2n**	75
15	4-pyridylmethyl	**1o**	**2o**	77
16	3-methylbenzyl	**1p**	**2p**	80
17	3-chlorobenzyl	**1q**	**2q**	81
18	phenyl	**1r**	**2r**	0
19	benzoyl	**1s**	**2s**	0

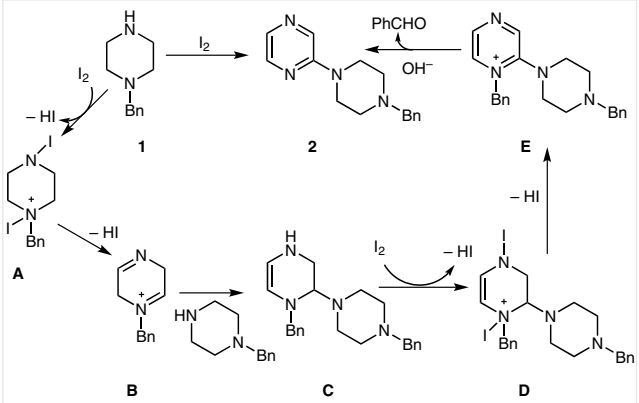
[a] Reaction conditions: substrate (10 mmol), I_2 (20 mmol), NaOAc (40 mmol) in MeCN (20 mL), heated at 70 °C.
[b] Isolated yield.



Scheme 2 Control experiments

To gain further insight into the reaction mechanism, several control experiments were performed with **1a** as model substrate (Scheme 2). When the model reaction was carried out under a nitrogen atmosphere, the product **2a** was yielded in 85% yield, indicating that the dioxygen in air might not make a contribution to the transformation in the present reaction. Furthermore, we added aniline (1.0 equiv) to the reaction system, resulting in a by-product, *N*-benzylaniline. Additionally, the yield rose up to about 1.2 times by adding piperazine (1.0 equiv) to the reaction system. On the basis of these preliminary results mentioned above together with the previous related literature,[16,17] a proposed mechanism is suggested in Scheme 3.

With the reaction of substrate **1a** as an example, we believe that the reaction begins with the formation of an *N*-iodioammonium intermediate (**A**) which eliminates two molecules of HI to give the iminium cation **B**. Ammonolysis of **B** provides the intermediate **C**. Obviously, secondary amines performed better in this step than the primary amines. Subsequently, further iodination of **C** leads to the formation of new iodioammonium intermediate **D**, which loses HI to give the intermediate **E**. Aqueous hydrolysis of intermediate **E** provides the desired product **2** with eliminating a molecule of benzaldehyde.



Scheme 3 Plausible mechanism

In summary, a novel and concise route to the synthesis of 2-(piperazin-1-yl)pyrazine derivatives via I_2-mediated one-pot reaction of *N*-alkyl piperazines has been developed.[18] This newly developed method gives access in a single step with a single material to 2-(piperazin-1-yl)pyrazines, which is not possible by any other reported method. This protocol is attractive and practical since cheap I_2 and NaOAc are employed and proceed in generally good yields and a broad range of functional groups tolerance. Considering these advantages, we believe that this methodology could attract attention for various applications in the field of medicinal chemistry and natural product chemistry. Additionally, based on a series of control experiments, plausible reaction mechanism was proposed.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588701.

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(18) **Experimental Procedures and Characterization Data; General Procedure for the Synthesis of Compound 2**: To a solution of substrate **1** (10 mmol) in MeCN (20 mL), iodine (5.1 g, 20 mmol) and NaOAc (3.3g, 40 mmol) were carefully added. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, the mixture was cooled and concentrated to provide the crude product which was purified by recrystallization from EtOH or by column chromatography using basic alumina. **2-(4-Benzylpiperazin-1-yl)pyrazine (2a)**: the product was obtained by recrystallization from EtOH as a white solid (1.13 g). Yield: 89%; mp 85–87 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.30 (d, *J* = 1.5 Hz, 1 H), 8.07 (dd, *J* = 2.7, 1.5 Hz, 1 H), 7.83 (d, *J* = 2.6 Hz, 1 H), 7.32–7.39 (m, 4 H), 7.23–7.29 (m, 1 H), 3.53–3.58 (m, 4 H), 3.52 (s, 2 H), 2.43–2.48 (m, 4 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.13, 141.90, 138.38, 132.88, 131.77, 129.37, 128.68, 127.48, 62.49, 52.60, 44.43. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_4$: 255.1604; found: 255.1614.