One-pot Synthesis of 3-Bromoimidazo[1,2-*a*]pyridine Derivatives Accompanied by Dimethyl Sulfoxide Oxidation

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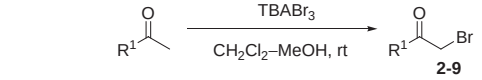
3-Bromoimidazo[1,2-*a*]pyridine derivatives have been directly synthesized from reaction of 2-aminopyridine derivative with α-haloketone derivatives in DMSO at room temperature, accompanied by DMSO oxidation.

Imidazo[1,2-*a*]pyridine (IP) derivatives have received considerable attention in the fields of organic chemistry and medicinal chemistry. They contain both a π-deficient pyridine ring and a π-excessive imidazole ring. Therefore, various reactions characteristic of each ring have been reported.[1] From the point of view of medicinal chemistry, these derivatives have been characterized as cyclin-dependent kinase inhibitors,[2] p38 MAP kinase inhibitors,[3] ligands for detecting β-amyloid plaques in the brain,[4] antiulcer molecules,[5] and hypnotics.[6] Recently, a report has also documented left–right patterning defects in zebrafish embryos with SCH28080,[7] which also contains an IP framework.[8] IP derivatives with these attractive properties possess a key functional group at the 3-position of the framework. Therefore, it is thought that development of novel synthetic method for introducing a variety of substituents to the 3-position of IP derivatives will lead to a new class of IP derivatives. Thus far, most synthetic methods for preparing 3-bromoimidazo[1,2-*a*]-pyridines have required two steps: formation of an IP framework under drastic conditions and subsequent bromination.[9] Therefore, development of direct synthesis of 3-bromoimidazo[1,2-*a*]-pyridines under mild conditions is an attractive theme. Herein, we report the one-pot synthesis of 3-bromoimidazo[1,2-*a*]pyridines **1a**–**1h** accompanied by dimethyl sulfoxide (DMSO) oxidation of α-bromoketones at room temperature (Chart 1).

α-Bromoketones **4**–**9**,[10] as the starting materials, were prepared in good yields by the reaction of acetophenones with an equimolar amount of tetra-*n*-butylammonium tribromide ($TBABr_3$) in dichloromethane–methanol at room temperature according to the literature procedure (Scheme 1).[11]

First, the reaction of 2-amino-3-(phenylmethyloxy)pyridine (**10**), which was prepared in 90% yield by O-benzylation[12] of commercially available 2-amino-3-hydroxypyridine using benzyl chloride at room temperature, with an equimolar amount of α-bromoketone **2** in DMSO at room temperature for 24 h, and subsequent treatment of the base gave the 3-nonsubstituted IP derivative **11a** in 84% yield, along with the 3-bromo IP derivative **1a** in 4% yield. Therefore, we examined conditions for obtaining the 3-bromo derivative as a main product. The results are summarized in Table 1.

In contrast to the reaction of **10** with an equimolar amount of **2**, the reaction of compound **10** with three equivalents of **2** in DMSO at room temperature for 12 h directly produced 3-bromo IP derivative **1a** as the main product in 63% yield, though IP compound **11a** and 3-methylthio IP derivative **12a** were also



1a–**1h**

a: R^1 = Ph, **b**: R^1 = CH_3, **c**: R^1 = 4-MeC_6H_4-, **d**: R^1 = 4-ClC_6H_4-, **e**: R^1 = 4-$MeOC_6H_4$-, **f**: R^1 = 4-$NO_2C_6H_4$-, **g**: R^1 = 4-FC_6H_4-, **h**: R^1 = 2-thienyl-

Chart 1.

2-9

2: R^1 = Ph, **3**: R^1 = CH_3, **4**: R^1 = 4-MeC_6H_4- (86%), **5**: R^1 = 4-ClC_6H_4- (85%), **6**: R^1 = 4-$MeOC_6H_4$- (90%), **7**: R^1 = 4-$NO_2C_6H_4$- (71%), **8**: R^1 = 4-FC_6H_4- (76%) **9**: R^1 = 2-thienyl- (83%)

Scheme 1. Preparation of α-bromoketone derivatives.

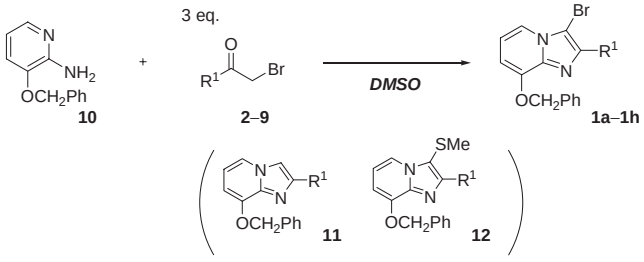
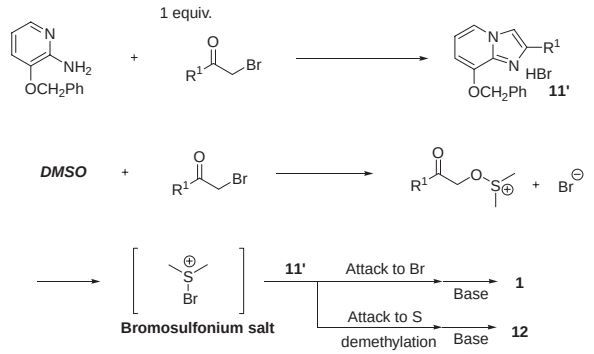


Table 1. One-pot synthesis of 3-bromoimidazo[1,2-*a*]pyridines in DMSO

Entry	Bromo-ketones	Reaction conditions		Yield/%[a]		
				1	**11**	**12**
1	**2** (1 equiv.)	rt, 24 h	**a**	4	84	—[b]
2	**2** (3 equiv.)	rt, 12 h	**a**	63	11	5
3	**2** (3 equiv.)	rt, 18 h	**a**	60	6	8
4	**2** (3 equiv.)	rt, 24 h	**a**	61	—	11
5	**2** (5 equiv.)	rt, 12 h	**a**	63	9	4
6	**2** (5 equiv.)	rt, 24 h	**a**	60	—	11
7	**2** (3 equiv.)	45 °C, 1 h	**a**	43	42	trace
8	**2** (3 equiv.)	45 °C, 3 h	**a**	56	—	15
9	**2** (3 equiv.)	60 °C, 1 h	**a**	54	trace	16
10	**3**	rt, 24 h	**b**	40	—	trace
11	**4**	rt, 24 h	**c**	57	—	12
12	**5**	rt, 24 h	**d**	61	—	10
13	**6**	rt, 24 h	**e**	58	—	12
14	**7**	rt, 24 h	**f**	63	—	14
15	**8**	rt, 24 h	**g**	59	—	10
16	**9**	rt, 24 h	**h**	62	—	13

[a]Isolated yield. [b]Not detected.



Scheme 2. A plausible mechanism for the formation of 3-bromoimidazo[1,2-*a*]pyridine derivatives.

obtained in 11 and 5% yields, respectively (Entries 1 and 2).[13] Elongation of the reaction time led to the increase of unfavorable product **12a** while compound **11a** disappeared (Entries 2–4). Further addition of α-bromoketone (five equivalents) was not effective for improving yield of products (Entries 5 and 6). Increasing temperature resulted in a decrease in the yield of **1a**, as compared with synthesis of compound **1a** under the condition of room temperature (Entries 7–9). This result would be due to the lower thermal stability of **1a**. Consequently, the conditions shown in Entry 4 were adopted as the optimum conditions.[14] The reaction of compound **10** with α-bromoketone derivatives **3**–**9** under this optimum conditions directly gave the desired products **1b**–**1h** in 40–63% yields, though unfavorable products **12a**–**12h** were also obtained, respectively (Entries 10–16). The lower yield for **1b** would be due to its instability and to the rapid decomposition of **3**.

A plausible mechanism for the reaction in this study is illustrated in Scheme 2. The reaction of 2-aminopyridine with an equimolar amount of α-bromoketone first yields salts of 3-non-substituted IP derivative **11′**. The reaction of an excess amount of α-bromoketone with DMSO as a solvent generates a bromosulfonium salt via an alkoxysulfonium salt. Attack by **11′** on the Br side of this reactive salt leads to the formation of **1**, along with dimethyl sulfide. On the other hand, attack on the S side and subsequent demethylation by bromide leads to the formation of **12**. Formation of dimethyl sulfide and α-hydroxyacetophenone during the experiment under the conditions shown in Entry 4 was confirmed. Reaction of **11′** in DMSO in the presence of **2** gave **1** and **12** in 73 and 9% yields, respectively.

In conclusion, we have demonstrated that the reaction of 2-aminopyridine derivatives with an excess amount of α-bromoketones proceeds smoothly to directly produce 3-bromoimidazo-[1,2-*a*]pyridine derivatives in moderate yields, along with corresponding 3-methylthio derivatives. Therefore, our method would be advantageous in terms of mild reaction at room temperature and one-pot procedure, compared with previous reports for the construction of title compounds.[9] Further study of the details of the reaction mechanism in this study and application of this method to other 2-amino-substituted heterocyclic compounds and α-haloketones, and their biological activities are now in progress.

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13 General procedure: To a solution of **10** (152 mg, 0.75 mmol) in dry DMSO (3.0 mL) was added **2** (447 mg, 2.25 mmol) at room temperature. The reaction mixture was stirred overnight at the same temperature, and then poured into ice-water. After being adjusted to pH 9 with saturated aqueous sodium carbonate, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with H_2O and brine, and then dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane–ethyl acetate, 4:1, v/v) to give **1a** (173 mg, 61%) as colorless needles, along with **12a** (29 mg, 11%) as yellow crystals. Selected data for **1a**: mp 98.5–99.0 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (2H, d, $J = 7.0$ Hz), 7.82 (1H, d, $J = 6.6$ Hz), 7.51–7.46 (4H, m), 7.40–7.31 (4H, m), 6.74 (1H, dd, $J = 6.6$ Hz, 7.9 Hz), 6.53 (1H, d, $J = 7.9$ Hz), 5.43 (2H, s). FAB-MS (NBA) m/z 380 $[M + H]^+$. **12a**: mp 98.5–99.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (2H, d, $J = 7.0$ Hz), 8.10 (1H, d, $J = 6.6$ Hz), 7.50–7.45 (4H, m), 7.39–7.31 (4H, m), 6.74 (1H, dd, $J = 6.6$ Hz, 7.9 Hz), 6.55 (1H, d, $J = 7.9$ Hz), 5.42 (2H, s), 2.24 (3H, s). FAB-MS (NBA) m/z 347 $[M + H]^+$.

14 Compounds **1** and **12** can be easily separated by column chromatography, though compounds **11** and **12** were difficult to separate due to comparable R_f value.

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