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Aminomethylation of Imidazoheterocycles with Morpholine

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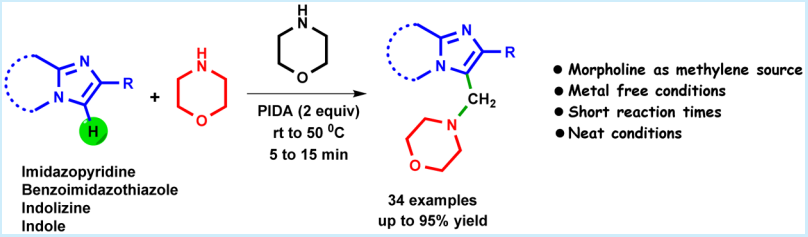
Supporting Information



ABSTRACT: A hitherto unreported aminomethylation occurs at C-3 of imidazopyridines with morpholine in the presence of (diacetoxyiodo)benzene at ambient temperature in short reaction times. This methodology is also applicable to indolizine, imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]thiazole, and indole. Interestingly, the aminomethylation involving morpholine as a source of methylene group is a new phenomenon. This protocol is of much potential for the synthesis of aminomethylated derivatives under mild reaction conditions.

Development of new methods for the formation of C−C and C−N bonds that avoid prefunctionalization is highly appreciable in modern organic chemistry.[1] Aminomethylation is one of the most important methods for the direct C−C and C−N bond forming reaction.[2] Conventionally aminomethylation is done by the Mannich reaction using formaldehyde as a methylene source.[3] Aminomethylated compounds are widely used as analgesics, antioplastics, and antibiotics and also as a synthetic precursor of many pharmaceutical active compounds.[4]

Imidazopyridine, a nitrogen containing fused heterocycle, shows wide range of biological activities.[5] These are broadly applicable in pharmaceutical chemistry as well as in material science.[6] Zolpidem, saripidem, alpidem, zolimidine, olprinone, and necopidem are some marketed drugs that contain this scaffold. Although in recent times various functionalization on imidazopyridines have been made,[7] aminomethylation is rare. Recently, a vanadium-catalyzed aminomethylation at C-3 position of imidazo[1,2-*a*]pyridine has been reported by Kumar et al. by using *N*-methylmorpholine oxide (NMO), which acts as coupling partner as well as the oxidant at high temperature in 1,4-dioxane solvent.[8] In continuing the development of new protocols for the functionalization of imidazoheterocycles,[9] herein we report a direct aminomethylation at C-3 of imidazopyridine with morpholine using (diacetoxyiodo)benzene (PIDA) under neat conditions (Scheme 1). To the best of our knowledge, this kind of transformation is unprecedented where morpholine itself acts as a source of methylene group.

We started our investigation by taking 2-phenylimidazo[1,2-*a*]pyridine (**1a**) as model substrate to find out the optimized reaction conditions as summarized in Table 1. Initially, the reaction was carried out by employing 1 equiv of morpholine (**2a**) and 1 equiv of PIDA at room temperature. Interestingly, aminomethylation occurred at C-3 of **1a** to afford 4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (**3a**) in 35% yield after 5 min (Table 1, entry 1). Inspired by this result, we increased the amount of morpholine from 1 equiv to 2 equiv, and yield was also increased to 57% (Table 1, entry 2). Next we used 2 equiv of PIDA in the presence of 2 equiv of morpholine, and the desired product was obtained in 92% yield (Table 1, entry 3). No further improvement of the yield was obtained with increasing the amount of both morpholine and PIDA (Table 1, entry 4). In all these cases, only a trace amount of aminated product **4a** was obtained.[9j] No product was formed in the presence of other oxidant such as $K_2S_2O_8$, *p*-benzoquinone (BQ), or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Table 1, entries 5−7). The yield of the reaction did not improve with increasing both reaction temperature and reaction time (Table 1, entry 8). Next we checked the effect of different common solvents such as 1,2-DCE, toluene, ethanol, 1,4-dioxane, and DMF. However, in the presence of solvents, aminomethylated product was obtained in very poor yields, whereas direct aminated product was formed as a major product (Table 1, entries 9−13). Finally, the use of PIDA (2 equiv) under solvent-free conditions was found to be the optimized reaction conditions (Table 1, entry 3).

With the optimized reaction conditions in hand, we showed the generality of this methodology by examining a variety of

Scheme 1. Aminomethylation of Imidazo[1,2-*a*]pyridine

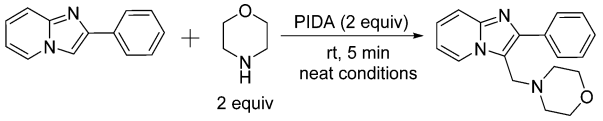


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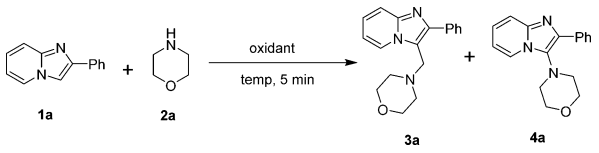
Table 1. Optimization of Reaction Conditions[a]



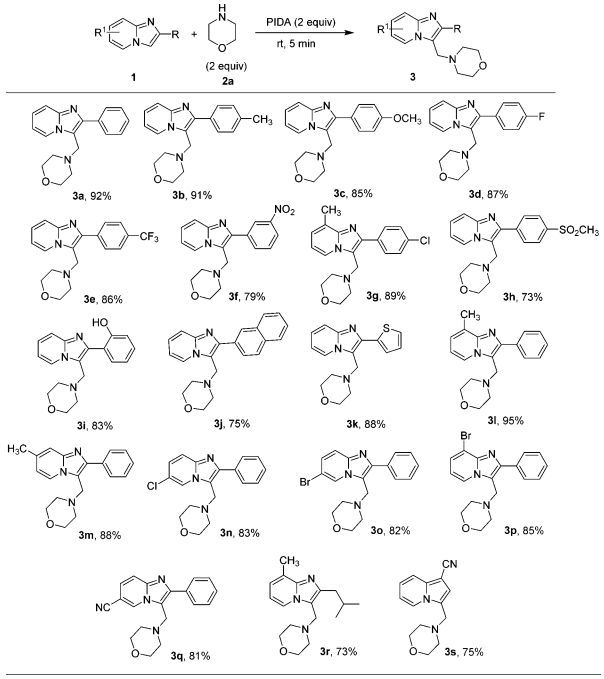
1a 2a 3a 4a

entry	2a (equiv)	oxidant (equiv)	solvent (2 mL)	yield of 3a (%)[b]	yield of 4a (%)[b]
1	1	PIDA (1)		35	trace
2	2	PIDA (1)		57	trace
3	2	PIDA (2)		92 (93)[c]	trace
4	3	PIDA (3)		89	trace
5	2	$K_2S_2O_8$ (2)			
6	2	BQ (2)			
7	2	DDQ (2)			
8	2	PIDA (2)		90[d]	trace
9	2	PIDA (2)	1,2-DCE	10	32
10	2	PIDA (2)	toluene	<5	67
11	2	PIDA (2)	ethanol	13	25
12	2	PIDA (2)	1,4-dioxane	trace	76
13	2	PIDA (2)	DMF	trace	trace

[a]Reaction conditions: all reactions were carried out on 0.2 mmol scale at room temperature for 5 min. [b]Isolated yields. [c]1 mmol scale. [d]Stirred at 50 °C for 1 h.

imidazo[1,2-*a*]pyridines as shown in Scheme 2. The presence of electron-donating substituents ($-CH_3$ and $-OCH_3$) at the

Scheme 2. Substrate Scopes[a,b]

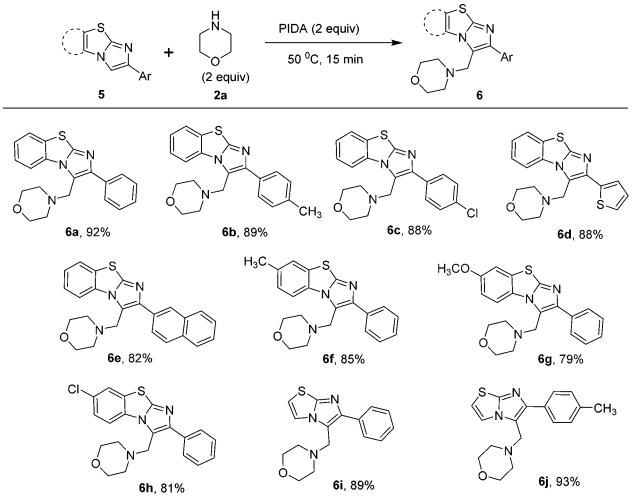


[a]Reaction conditions: 0.2 mmol of **1** and 2 equiv of **2a** in the presence of 2 equiv PIDA at room temperature for 5 min. [b]Isolated yields.

phenyl ring of imidazo[1,2-*a*]pyridines reacted with morpholine to give excellent yields of the desired products (**3b** and **3c**). Electron-withdrawing groups (−F, $-CF_3$, $-NO_2$, and −Cl) containing imidazo[1,2-*a*]pyridines also worked well (**3d**−**3g**). It is notable that marketed drug zolimidine also produced the aminomethylated product in good yield (**3h**). Hydroxy-substituted phenyl ring of imidazo[1,2-*a*]pyridine also successively gave the desired product without any difficulties (**3i**). Both naphthyl and heteroaryl substituted imidazopyridines also well tolerated (**3j** and **3k**). Next we checked the effect of substituent at the pyridine ring of imidazo[1,2-*a*]pyridine. Presence of both electron-releasing and electron-withdrawing substituents ($-CH_3$, −Cl, −Br, and −CN) at the pyridine ring afforded the desired products in excellent to good yields (**3l**−**3q**). Isopropyl substituted (C-2) imidazo[1,2-*a*]pyridine also reacted very smoothly (**3r**). It is noteworthy to mention that indolizine-1-carbonitrile was also aminomethylated under the present reaction conditions without any difficulties (**3s**).

To extend the scope of our methodology, we carried out the reaction with other imidazoheterocycles (**5**) such as imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole (Scheme 3). In all cases, aminomethylated products were obtained in excellent yields (**6a**−**6j**) at 50 °C.

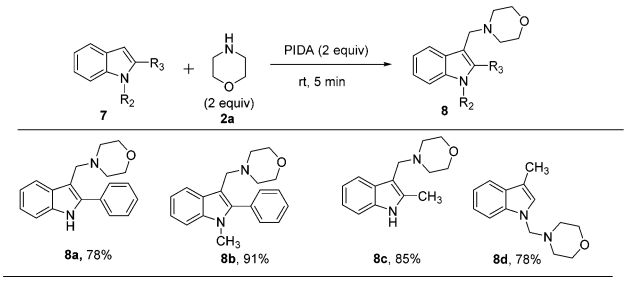
Scheme 3. Coupling between Imidazobenzothiazole and Benzothiazole with Morpholine[a,b]



[a]Reaction conditions: 0.2 mmol of **5** and 2 equiv of **2a** in the presence of 2 equiv PIDA at 50 °C for 15 min. [b]Isolated yields.

Next we checked the practicability of this method on the indole moiety (Scheme 4). Simple indole did not provide the desired product under the optimized reaction conditions. However, 2-substituted indole reacted very smoothly with morpholine to afford the desired products in good yields (**8a**−

Scheme 4. Substrate Scopes[a,b]



[a]Reaction conditions: 0.2 mmol of **7** and 2 equiv of **2a** in the presence of 2 equiv of PIDA at room temperature for 5 min. [b]Isolated yields.

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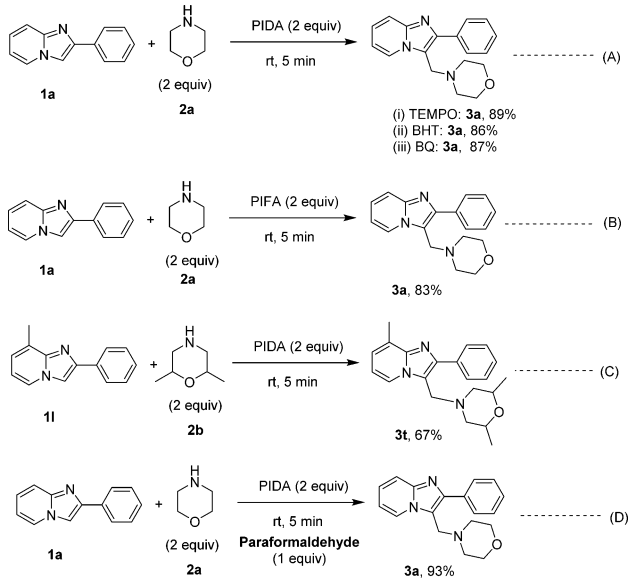
8c). In case of 3-methylindole, aminomethylation took place at nitrogen center of the indole moiety (8d).

To get a better understanding of the mechanistic pathway of the reaction, few mechanistic experiments were carried out (Scheme 5). The reaction did not hamper in the presence of

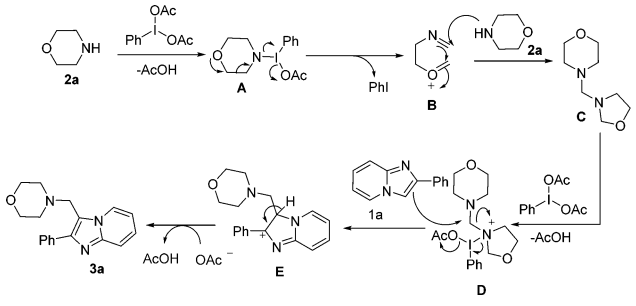
Scheme 5. Control Experiments



radical scavengers such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methyl phenol (BHT), and BQ (Scheme 5, eq A). This result suggested that the reaction probably followed an ionic pathway. In the presence of PIFA, the reaction also proceeded very smoothly, from which it can be proposed that PIDA is not source of $-CH_2$ group for aminomethylation (Scheme 5, eq B). The aminomethylation was also carried out using 2,6-dimethylmorpholine (**2b**) (Scheme 5, eq C). Formation of 2,6-dimethyl-4-((8-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (**3t**) indicated that the source of methylene group is the C-3 of morpholine. No improvement of the yield was observed with the addition of paraformaldehyde (1 equiv) in the reaction mixture (Scheme 5, eq D). This result signified that the reaction did not proceed through the formation of formaldehyde from morpholine.

On the basis of the control experiments and our previous experiences on the functionalization of imidazo[1,2-*a*]-pyridines,[9] a proposed reaction mechanism is outlined in Scheme 6. Probably at the first step *N*-iodoamido species (**A**) is formed by the reaction between morpholine and PIDA.

Scheme 6. Plausible Mechanistic Pathway



Through the ring opening, the intermediate **A** is converted to the intermediate **B**, which is readily coupled with morpholine to give the intermediate **C**. Subsequently, the intermediate **C** is oxidized by PIDA to the intermediate **D**, which reacts with imidazo[1,2-*a*]pyridine to produce the aminomethylated product **3a** via the formation of **E**.

The single crystal X-ray analysis of **3g** was performed to confirm the structure of the 4-((2-(4-chlorophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (Figure 1).[10]

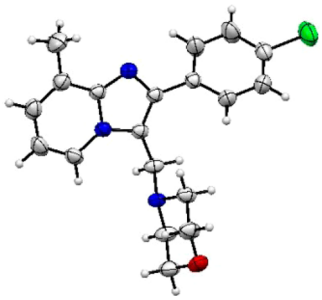


Figure 1. Single crystal XRD structure of compound **3g**.

In conclusion, unprecedented aminomethylated derivatives were obtained by the coupling between imidazoheterocycles and morpholine using PIDA as an oxidant at ambient temperature under neat conditions in short reaction times. Remarkably, this is the first report for the employment of morpholine as methylene source for aminomethylation reaction. The reaction exhibits good functional group tolerance with a variety of heterocycles such as imidazo[1,2-*a*]pyridine, indolizine, imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]-thiazole, and indole. Certainly, the present strategy opens a new door to synthesize aminomethylated derivatives under the mild reaction conditions and is of much potential in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01594.

Additional data, spectral data of all compounds, scanned spectra of new compounds (PDF)
CIF information on **3g** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) Further information can be found in the CIF file. This crystal data were deposited in the Cambridge Crystallographic Data Centre and assigned as CCDC 1551255.

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