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N-Methylation of Amines with Methanol at Room Temperature

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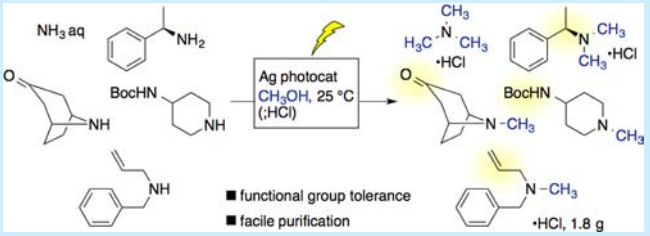
Supporting Information

ABSTRACT: N-Methylation of amines with methanol proceeds at room temperature in the presence of a silver-loaded titanium dioxide (Ag/TiO_2) photocatalyst under UV–vis light irradiation. This method allows facile synthesis/isolation of *N*-methylamines bearing various functional groups including *N*-benzyl, *N*-allyl, *N*-Boc, hydroxyl, ether, acetal, carboxamide, formamide, and olefin groups.



N-Methylamines are widely used as pharmaceuticals, dyes, detergents, and synthetic intermediates.[1,2] Although numerous stoichiometric[3,4] and catalytic[5−7] methods for N-methylation of amines are available, methanol (CH_3OH) as a methylating agent[8−10] is challenging yet advantageous in that (1) it does not require addition of acidic or reducing agents (e.g., formic acid or $NaBH_4$ in the case of reductive amination), allowing selective methylation of amines bearing acid- or redox-sensitive functional groups, and (2) the sole byproduct is water, which simplifies purification. However, known methods using heterogeneous or transition metal catalysts require high reaction temperature (100−400 °C) not useful for volatile CH_3OH (bp 65 °C), and reducible functional groups such as C−C and C−O unsaturated bonds are not generally tolerated.[8−10] We report here N-methylation of amines with CH_3OH using a photocatalyst, silver-loaded titanium dioxide (Ag/TiO_2, Scheme 1). This method allows N-methylation of a wide range of amines in anhydrous or aqueous CH_3OH at room temperature without loss of acid-, base-, or redox-sensitive functional groups.

Photocatalytic N-methylation of amines was reported by Ohtani and Kagiya's group in 1986: N,N-dimethylation of benzylamine with CH_3OH in the presence of Pt/TiO_2 at room temperature for 10 h gave *N*,*N*-dimethylbenzylamine in a low yield (28%).[11] This method has been employed in a system for methylation of anilines using microreactors (reaction time: 90 s, 23% yield).[12] Au/TiO_2 has also been found to promote photocatalytic N-monoalkylation of aniline with alcohols but is not effective for N-methylation.[13a] Pd/TiO_2 has been reported as a photocatalyst for N-benzylation, N-ethylation, and N-butylation of simple amines, but its effectiveness for N-methylation remains unclear.[13b] Overall, the functional group compatibility of photocatalytic N-methylation of amines has been poorly investigated so far, though chemoselectivity is critically important for selective organic synthesis.[14] We recently found that reducible functional groups such as C−C multiple bonds are compatible with photocatalytic transformations of alcohols, including dehydrogenation of primary alcohols to aldehydes[15] and transfer hydrogenolysis of allyl alcohol to propylene.[16] Thus, we envisaged that the photocatalytic N-methylation of amines with CH_3OH, if a suitable photocatalyst could be identified, would provide a high degree of functional group tolerance that would be difficult to achieve with thermal methods.

We first investigated the photocatalytic activity of metal-loaded TiO_2 for the N-methylation of a functionalized amine. We chose *N*-allylbenzylamine (**2a**, Scheme 1) as a model substrate because **2a** contains *N*-allyl and *N*-benzyl moieties that allow us to monitor the tolerance of acid- and redox-sensitive functional groups.[17] Each metal (Ag, Au, Pd, or Pt) was loaded on a TiO_2 surface by impregnating TiO_2 (Aeroxide P25) with an aqueous solution of metal salts, followed by reduction with $NaBH_4$ under aqueous conditions.[16] The metal contents were determined by

Scheme 1. Photocatalytic N-Methylation of Primary and Secondary Amines (1 and 2) Using Methanol (2a and 3a: FG = CH_2=$CHCH_2$; R = $C_6H_5CH_2$)

FG = functional group

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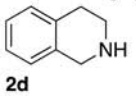
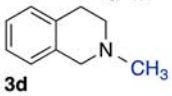
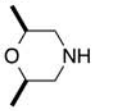
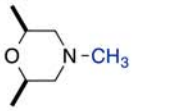
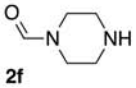
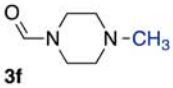
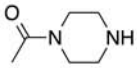
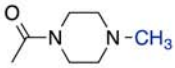
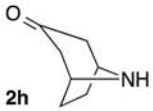
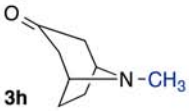
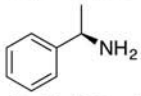
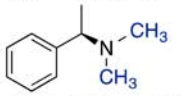
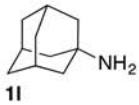
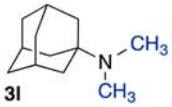
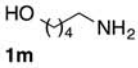
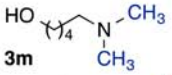
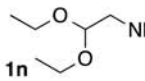
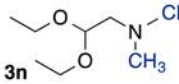
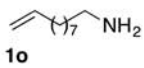
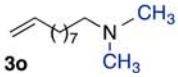
inductively coupled plasma atomic emission spectrometry (ICP-AES, Table S1). To our delight, silver-loaded TiO_2, Ag/TiO_2, served as an excellent photocatalyst for N-methylation of **2a** with CH_3OH (Table S2, entry 1). Irradiation of a mixture of **2a** (2.0 mmol), CH_3OH (20 mL, 490 mmol), and Ag/TiO_2 (43 mg, 4 wt % Ag, Ag = 0.9 mol %) with a UV–vis light (λ = 300–470 nm, 300 W Xe lamp with a UV cold mirror) at 25 °C for 10 h gave *N*-allyl-*N*-methylbenzylamine (**3a**) in quantitative yield, as determined by gas chromatography. The allyl and benzyl moieties of **2a** and **3a** remained intact during the irradiation. Removal of the catalyst by centrifugation followed by addition of an ether solution of hydrogen chloride afforded the HCl salt of **3a** (94% yield) as an analytically pure compound. This result was reproducible, and **3a**·HCl was obtained in 88–96% isolated yield in several iterative experiments. The Ag (4 wt %)/TiO_2 catalyst was characterized by high-resolution transmission electron microscopy, diffuse reflectance spectroscopy, X-ray diffraction, and X-ray photoelectron spectroscopy (Figures S1–S4). The Ag/TiO_2 catalyst can be stored under atmospheric conditions at 25 °C and is stable at least for 3 months. In contrast to Ag/TiO_2, N-methylation using Au/TiO_2, Pd/TiO_2, or Pt/TiO_2 catalyst was less efficient due to side reactions such as reduction of the double bond and cleavage of the *N*-allyl group (Table S2, entries 2–4). Both Ag and TiO_2 were found to be necessary for selective N-methylation of **2a**. Ag/TiO_2 catalysts containing less Ag (0.9 or 0.5 wt %) were less reactive than Ag (4 wt %)/TiO_2 (entries 5 and 6), and the reaction barely took place in the absence of Ag (entry 7). Use of Ag/γ-Al_2O_3 (entry 8) or $AgNO_3$ (entry 9) was consistently ineffective. Light irradiation was essential for the Ag/TiO_2-catalyzed N-methylation of amines, and N-methylation of **2a** barely proceeded without UV–vis light irradiation under conditions otherwise identical to those in entry 1 (entry 10). N-methylation proceeded under both acidic and basic conditions. Although the reaction was slower in the presence of a base (*t*-C_4H_9OK, entry 11), addition of an acidic additive (*p*-$CH_3C_6H_4SO_3H$) did not significantly change the outcome (entry 12). The Ag/TiO_2-catalyzed N-alkylation was found to be scalable, with 10 mmol of **2a** being successfully converted to 1.8 g of the desired product **3a**·HCl (92% isolated yield, entry 13).

Table 1 summarizes the results of photocatalytic N-methylation of various amines. The products were isolated and analyzed as hydrochloride salts (**3**·HCl) unless otherwise noted. Both acyclic and cyclic secondary amines were easily converted to the corresponding *N*-methylamines in good to excellent yields (entries 1–7). In the case of aliphatic primary amines, N,N-dimethylation took place smoothly (entries 8–14). The presence of carbonyl functionalities in formamide **2f**, acetamide **2g**, and ketone **2h** was tolerated (entries 5–7). Notably, the carbonyl group in the ketone **2h** remained intact even though a ketone carbonyl group is not effectively tolerated under typical conditions of reductive amination using $NaBH_4$ or $NaHB(O_2CCH_3)_3$.[3,18] The absolute configuration at the benzylic carbon of (*R*)-**1k** was retained (*S*:*R* ratio of the product **3k** was 4:96, entry 10). N-Alkylation of amino alcohol **1m** took place with CH_3OH exclusively; the hydroxyl group of **1m** did not serve as an alkylating agent and remained intact (entry 12). The acid-sensitive acetal in **1n** and carbon–carbon double bond distal from the amino group in **1o** were also tolerated (entries 13 and 14).

Ag/TiO_2-catalyzed N-methylation was sluggish or inefficient for more electron-deficient amines such as aniline, tetrahydroquinoline, indole, carboxamides, and *N*-tosyl amides under analogous reaction conditions. With this preliminary information in hand, we next examined selective N-methylation of *N*-butoxycarbonyl (Boc)-protected diamines (**2p** and **1q**) (Scheme 2). The N-methylation took place exclusively at the amino functionalities, which are more basic than carbamates, yielding the corresponding amines **3p** and **3q** with preservation of the acid-labile NHBoc functionalities.

More polar substrates can be efficiently N-methylated using water as a cosolvent (Scheme 3). Irradiation of a mixture of aqueous ammonia and methanol in the presence of the Ag (4 wt %)/TiO_2 catalyst allowed trimethylation of ammonia to give trimethylamine (**3r**), and the product could be isolated as **3r**·HCl

Table 1. Photocatalytic N-Methylation of Amines[a]

entry	reactant	product	*t* (h)	yield (%)[b]
	R_2N–H	R_2N–CH_3		
1	**2b** (R = *n*-C_4H_9)	**3b** (R = *n*-C_4H_9)	6	96
2	**2c** (R = *c*-C_6H_{11})	**3c** (R = *c*-C_6H_{11})	6	94
3	 **2d**	 **3d**	10	95
4	 **2e**	 **3e**	10	80
5	 **2f**	 **3f**	10	88[c]
6	 **2g**	 **3g**	10	97
7	 **2h**	 **3h**	10	84[c]
	R–NH_2	R–$N(CH_3)_2$		
8	**1i** (R = *n*-C_8H_{17})	**3i** (R = *n*-C_8H_{17})	6	94
9	**1j** (R = $C_6H_5CH_2$)	**3j** (R = $C_6H_5CH_2$)	6	93
10	 (*R*)-**1k** (*S*:*R* = 2:98[d])	 (*R*)-**3k** (*S*:*R* = 4:96[e])	10	85
11	 **1l**	 **3l**	10	92
12	 **1m**	 **3m**	10	94
13	 **1n**	 **3n**	10	55[c,f]
14	 **1o**	 **3o**	10	79[c,f]

[a]Conditions: **1** or **2** (2.0 mmol), CH_3OH (20 mL), Ag (4 wt %)/TiO_2 (43 mg), 300 W Xe lamp with UV cold mirror (λ = 300–470 nm), Ar (1 atm), 25 °C, unless otherwise noted. [b]Isolated yield of **3**·HCl after the addition of HCl in diethyl ether (1.2 equiv). [c]Isolated yield of **3**. [d]Indicated by the supplier. [e]Determined by HPLC analysis. [f]Decreased yields due to the volatile nature of the products.

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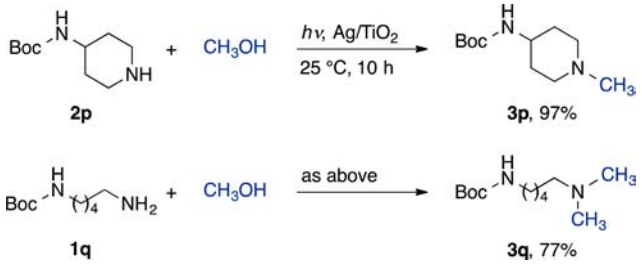
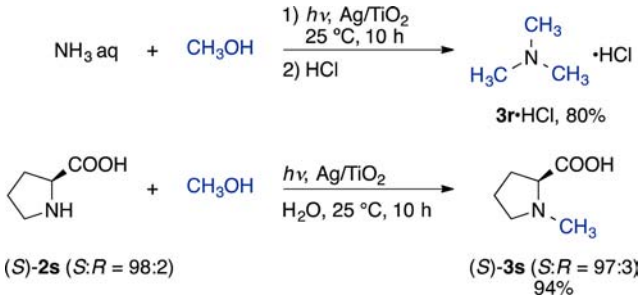
Scheme 2. N-Methylation of Amines without Loss of *N*-Boc-Protected Amino Functionalities



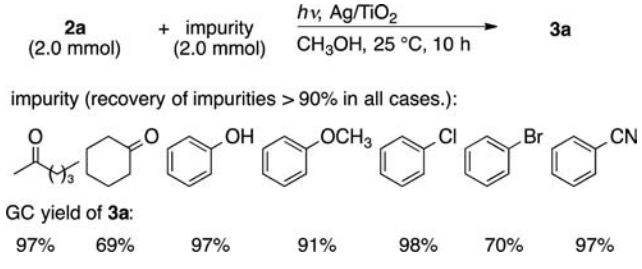
Scheme 3. Methylation under Aqueous Conditions



in 80% yield. Analogously, L-proline [(*S*)-**2s**, *S*:*R* ratio = 98:2] was N-methylated to give *N*-methylproline [(*S*)-**3s**] in 94% yield with retention of the chirality at the α position (*S*:*R* ratio of **3s** = 97:3).

Further functional group compatibility was investigated by N-methylation of **2a** in the presence of an equimolar amount of impurities such as acyclic and cyclic ketones: phenol and its methyl ether, aryl chloride and -bromide, and benzonitrile (Scheme 4). In all of these cases, **3a** was obtained in good to

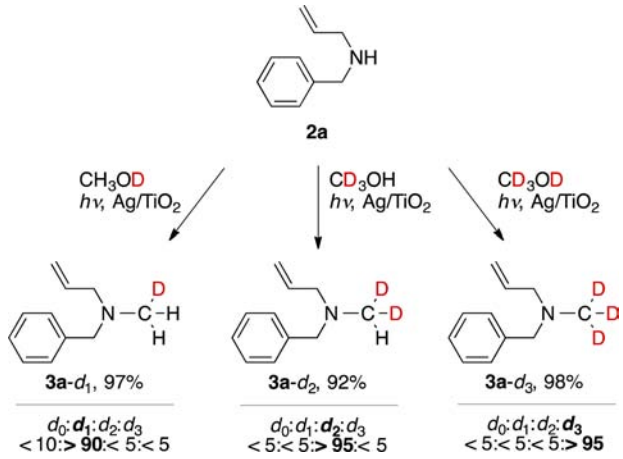
Scheme 4. Compatibility of Functional Groups



excellent yield (69−98%) without being significantly affected by impurities, which were recovered in > 90% yield. In the presence of iodobenzene, the N-methylation was sluggish but yielded **3a** in 22%, with the recovery of iodobenzene being 77%. The desired **3a** was not detected when nitrobenzene was added as an impurity, the recovery of which was 29%.

Synthesis of isotope-labeled amines is an important requirement in medical applications because they are frequently used for in vivo studies in animals and humans, for example, to examine drug metabolism or enzyme mechanisms.[19] The current method enables concise synthesis of mono-, di-, or trideuterated *N*-methylamines **3a**-d_{1-3} simply by using deuterated methanols in place of CH_3OH (Scheme 5). Reaction of **2a** with CH_3OD gave monodeuterated *N*-methylamine **3a**-d_1 as an exclusive product. Use of CD_3OH and CD_3OD resulted in a clean formation of di- and trideuterated *N*-methylamines **3a**-d_2 and **3a**-d_3, respectively.

Scheme 5. Synthesis of Deuterated *N*-Methylamines[a]



[a]Conditions: **2a** (1.0 mmol), deuterated methanols (1 mL), Ag (4 wt %)/TiO_2 (22 mg), 300 W Xe lamp with UV cold mirror (λ = 300−470 nm), Ar (1 atm), 25 °C, 10 h in Schlenk tubes. Yields are shown as isolated yields of the HCl salts. Ratios of **3a**/**3a**-d_1/**3a**-d_2/**3a**-d_3 were determined by ^{1}H NMR analysis of crude products (Figure S5A).

These results are consistent with NMR and mass spectrometric analyses of **3a** and **3a**-d_{1-3} (Figure S5).

In summary, we demonstrated the photocatalytic N-methylation of amines with CH_3OH at ambient temperature under anhydrous/aqueous and acidic/neutral/basic conditions, where the presence of reducible C−C and C−O bonds was tolerated. We envisage that improvement of this photocatalytic system will provide a useful tool for late-stage functionalization of pharmaceutically important chemicals,[14] as well as rapid synthesis of ^{11}C-labeled pharmaceuticals for positron emission tomography by using $^{11}CH_3OH$ and microreactors.[20]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, figures and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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