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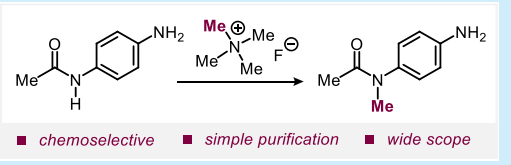
Selective Methylation of Amides, *N*-Heterocycles, Thiols, and Alcohols with Tetramethylammonium Fluoride

Hong-Gang Cheng, Maoping Pu, Gourab Kundu, and Franziska Schoenebeck*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

Supporting Information

ABSTRACT: We herein disclose the use of tetramethylammonium fluoride (TMAF) as a direct and selective methylating agent of a variety of amides, indoles, pyrroles, imidazoles, alcohols, and thiols. The method is characterized by operational simplicity, wide scope, and ease of purification. Our computational studies suggest a concerted methylation−deprotonation as the preferred reaction pathway.



Although the methyl group is the smallest alkyl group, its incorporation can greatly modulate the solubility, hydrophilicity, and conformation of polymers, proteins, drug candidates, etc., thus leading to a drastic improvement of their biological activity, pharmacokinetic profile, and physical properties.[1] This so-called "magic methyl effect" renders methylation as one of the most popular structural modifications in medicinal chemistry. Indeed, a survey by Njardarson on the top-sold 200 pharmaceuticals in 2018 shows that over 70% of small-molecule drugs contain at least one methyl group,[2] with representative examples shown in Figure 1a. Consequently, the development of efficient strategies for the selective introduction of methyl groups into organic molecules is of significant interest.

In this context, the methylation of amides is of particular importance as these are ubiquitous motifs in a range of medically important compounds.[3] As such, substantial efforts have been devoted to this field (see Figure 1).[4] The methylation of amides is traditionally done with frequently unstable, volatile, or toxic methylating agents such as iodomethane,[5] dimethyl sulfate,[6] or chloromethyldimethylsilyl chloride[7] and frequently requires an excess of a strong base. Alternative strategies include the reductive methylation with formaldehyde as a methylcarbon source[8] or the transition-metal-catalyzed methylation of amides with methanol.[9] While the former method requires an excess of reducing agents as well as strong acids (e.g., trifluoroacetic acid), which limits applicability, the latter suffers from relatively low conversion and/or harsh reaction conditions. In the past decade, the employment of peroxides[10] or $PO(OMe)_3$[11] as methylation reagents also gained popularity; these methods are in need of specialized transition-metal catalysts, however, and display relatively narrow scope.

As such, there is a continuing demand for a safe, practical, and metal-free methylation methodology of amides, particularly paired with high chemoselectivity.

We herein report the efficient and chemoselective methylation of amides as well as *N*-heterocycles, thiols, and alcohols, employing tetramethylammonium fluoride (TMAF)[12] as the methyl group source. We started our

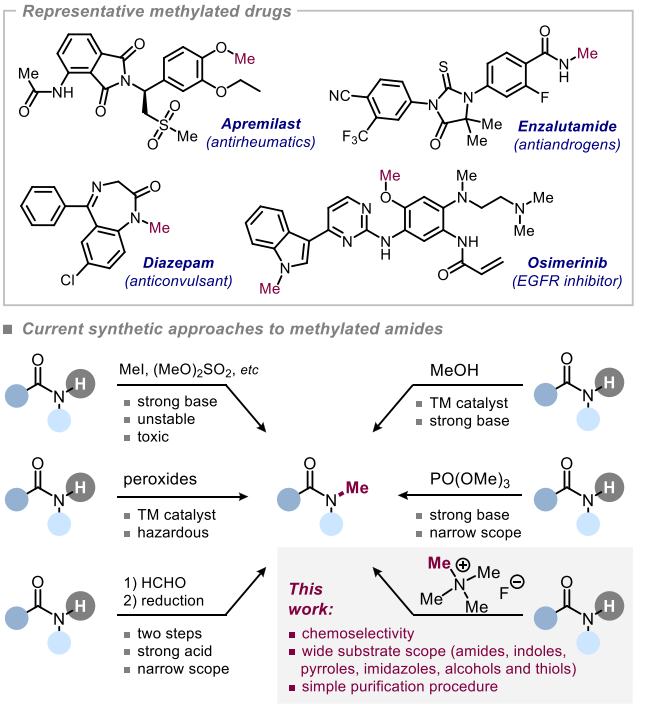


Figure 1. Representative drugs containing methyl groups (top) and common methylation strategies of amides (bottom).

investigations with the methylation of *N*-phenylacetamide (**1**), see Table 1. After extensive survey of the reaction parameters,[13] the optimal conditions were identified as TMAF (2.5 equiv) in toluene (0.4 M) at 100 °C, wherein the desired *N*-methyl-*N*-phenylacetamide (**2**) was obtained in 95% yield after 12 h (entry 1). A series of control experiments was also conducted: decreasing the temperature to 80 °C led to a slightly lower yield and required longer reaction times. At

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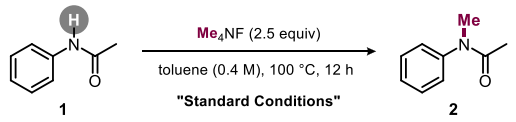
Table 1. Optimization of the Reaction Conditions[a]



entry	change from the standard conditions	yield (%)[b]
1	none	95 (92)[c]
2	80 °C instead of 100 °C	93[d]
3	rt instead of 100 °C	0[d]
4	NMP instead of toluene	95
5	DMF instead of toluene	70
6	CH_3CN instead of toluene	57
7	Me_4NCl instead of Me_4NF	0[d]
8	Me_4NBr instead of Me_4NF	0[d]
9	Me_4NCl and KF instead of Me_4NF	0[d]

[a]Reactions were performed on a 0.2 mmol scale. [b]Yields were determined by GC analysis using dodecane as the internal standard. [c]Isolated yield is shown in parentheses. [d]24 h.

room temperature, no reaction took place (entries 2 and 3). The polar solvent NMP proved to be as equally effective for this reaction as toluene (entry 4). Moderate yields could also be obtained when DMF or CH_3CN were used as the solvent (entries 5 and 6). Toluene was selected as the solvent due to the added operational simplicity of the purification procedure, as the excess TMAF and the only byproduct, Me_3NHF, will precipitate upon cooling to room temperature. This allows for final purification via a simple filtration over a small pad of silica. The fluoride anion in TMAF is critical for this process, as the switching of fluoride to bromide or chloride both resulted in no formation of desired product (entries 7 and 8).[14] A combination of tetramethylammonium chloride (Me_4NCl, 2.5 equiv) and KF (2.5 equiv) instead of TMAF also failed to give any product (entry 9).

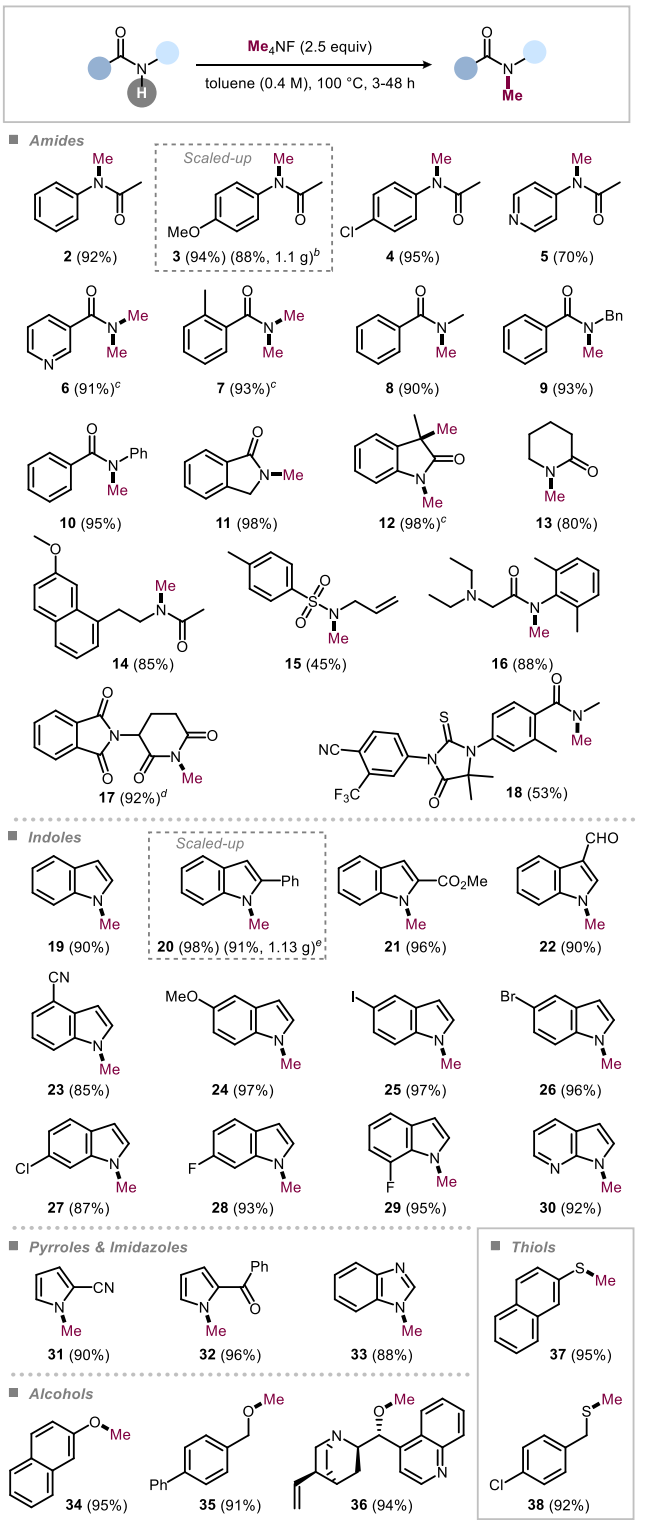
With the optimized reaction conditions in hand, we subsequently examined the substrate scope (Scheme 1). Employing TMAF as the methylation reagent, an array of amides, including acyclic amides (**2**–**10**, **14**), cyclic amides (**11**–**13**), and sulfonamide (**15**) were found to react efficiently, providing the desired methylated amides in moderate to excellent yields. Moreover, aliphatic, aromatic, and heterocyclic substituents were tolerated. Notably, when 3-methylindolin-2-one was employed as substrate, methylation occurred at both N1 and C3 position (product **12**), which demonstrates that the method is also amenable for C–H methylation, provided the site is sufficiently acidic.

We next investigated the potential of our method in late-stage methylation of bioactive compounds. We successfully methylated the anesthetic lidocaine (**16**),[15] the drug thalidomide (**17**),[16] and anticancer agent enzalutamide (**18**).[17]

We subsequently explored the scalability and performed the reaction on a 7.0 mmol scale, which led to the successful preparation of product **3** in 1.1 g (88% yield).

We next tested the performance of TMAF to methylate functional groups other than amides. As shown in Scheme 1, a number of substituted 1*H*-indoles were efficiently methylated to **19**–**30**, independent of their respective substitution patterns, tolerating substituents at C2 (**20** and **21**), C3 (**22**), C4 (**23**), C5 (**24**–**26**), C6 (**27** and **28**), and C7 (**29**) of the indole ring. A range of functional groups such as ester (**21**), aldehyde (**22**), cyano (**23**), methoxy (**24**), iodo (**25**), bromo (**26**), chloro (**27**), and fluoro (**28** and **29**) were well-tolerated, providing handles for further diversification.

Scheme 1. Scope of the Amides[a]



[a]Conditions: Substrate (0.4 mmol), TMAF (93.2 mg, 1.0 mmol), in toluene (1.0 mL) at 100 °C. Isolated yields are shown. [b]The reaction was performed on a 7.0 mmol scale. [c]5.0 equiv of TMAF. [d]NMP was used instead of toluene. [e]The reaction was performed on a 6.0 mmol scale.

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Notably, a scale-up operation (6.0 mmol) of this methylation procedure was successfully performed to obtain 1.13 g of product **20** (91% yield).

Moreover, pyrroles and imidazoles could also be converted to the corresponding methylated products in 88−96% yields (**31**−**33**). Similarly, methylations of phenol (**34**), alcohols (**35** and **36**), and thiols (**37** and **38**) proceeded equally smoothly to give the corresponding methylated products in excellent yields, highlighting the generality of this process.

We then turned our attention to substrates with multiple potential reactive sites. To our delight, when attempting to methylate substrates that contained both an amide and an aromatic primary amine functionality (**39** and **40** in Figure 2a),

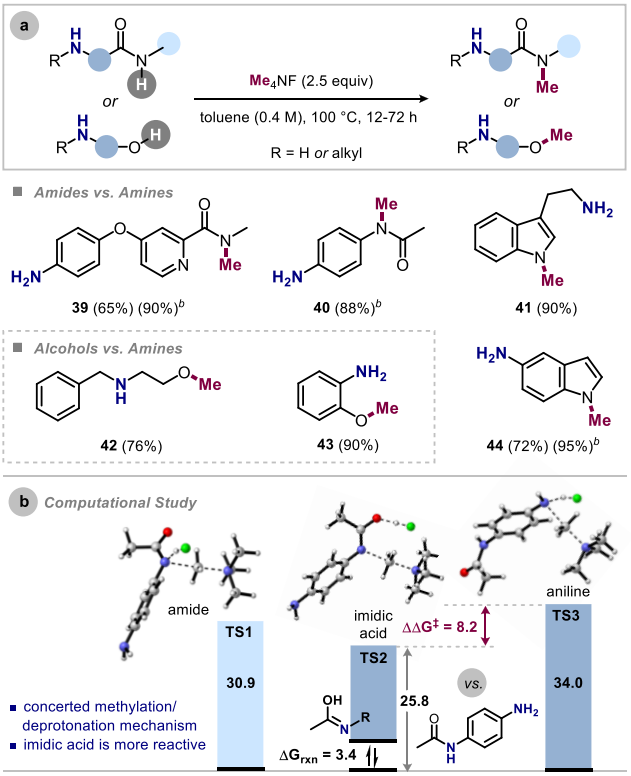

Figure 2. (a) Chemoselective methylations with TMAF. [a]Conditions: Substrate (0.4 mmol), TMAF (93.2 mg, 1.0 mmol), in toluene (1.0 mL) at 100 °C for 12−72 h. Isolated yields are shown. [b]NMP (1 mL) at 160 °C. (b) Computational study. Energies refer to Gibbs free energy activation barriers (in kcal/mol) calculated at the M06-2x/def2-TZVP//M06-2*x*/6-31G(d,p) level of theory.

the methylation exclusively occurred at the amide NH site, regardless of the number of employed equivalents of TMAF, giving products **39** and **40** in 90 and 88% yield, respectively. For comparison, with conventional methodology, **40** was previously prepared in a three-step sequence.[18]

Also in the cases of **41**−**44**, the corresponding methylation occurred at the indole NH site or hydroxyl site selectively in high yields, leaving the primary or secondary amine site completely untouched.

To gain insight into the mechanism, we turned to DFT calculations (Figure 2b). Following our previous studies where we demonstrated that a methyl can be transferred with relatively low activation barrier from NMe_4^+ to amines, albeit endergonically,[19] we tested whether the methyl transfer to amides could potentially occur in an analogous fashion, i.e. via a direct methyl cation transfer from TMAF. However, both aromatic and alkyl amides show prohibitively high activation free energy barriers (>45 kcal/mol) for transferring a CH_3 to NH.[13]

Notably, our control experiments (Table 1) showed that fluoride plays a decisive role, as using the corresponding chloride or bromide salts (i.e., TMACl or TMABr) resulted in no reaction. Moreover, it has previously been shown that fluoride can act as a base.[20] Hence, in the search for an alternative mechanism, we considered a concerted deprotonation (by F^-) and methyl transfer (from NMe_4^+) (see Figure 2b). The corresponding activation free energy barrier associated with this process is 30.9 kcal/mol. In this context, we also considered that the amide could tautomerize to the imidic acid, which is 3.4 kcal/mol higher in energy than the amide. Interestingly, despite the free energy penalty for tautomerization, overall, the concerted methylation/deprotonation is favored via the imidic acid tautomer by $\Delta\Delta G^{\ddagger} = 5.1$ kcal/mol over direct reaction of the amide (see Figure 2b, TS2). Moreover, the corresponding methylation at the primary amine site (Figure 2b, TS3) is more than 8 kcal/mol higher than methylation via TS2, which is in line with the observed exclusive chemoselectivity.

In conclusion, we described the employment of tetramethylammonium fluoride as a highly efficient, practical, direct, and chemoselective methylation reagent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04400.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of the new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: franziska.schoenebeck@rwth-aachen.de

ORCID

Franziska Schoenebeck: 0000-0003-0047-0929

Notes

The authors declare no competing financial interest.

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