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Efficient Synthesis of 2-Arylpropionitriles Via Selective Monomethylation of Aryl Acetonitriles Using an Easy to Handle Methylation Agent

Eleni Papaplioura,[a] Johanna Templ,[a] Nina Wildhack,[a] and Michael Schnürch*[a]

A convenient and safe methylation protocol employing quaternary ammonium salts ($PhMe_3NI$) as alternative methylating agents for the selective α-methylation of arylacetonitriles is presented. This approach allows for the selective α-methylation of arylacetonitriles, overcoming the limitations of existing techniques, while offering a practical and sustainable solution for late-stage functionalization in medicinal chemistry. The straightforward and safe nature of this methodology makes it particularly well-suited for applications in drug discovery. In our report, we present a diverse set of 18 examples, achieving yields of up to 76%.

Introduction

Nitrile-containing pharmaceuticals are widely prescribed drugs, with broad bioactive potential, for treating various conditions.[1,2] Specifically, aryl acetonitriles are versatile compounds and important precursors in pharmaceutical manufacturing.[1] Anastrazole, Galopamil, and Verapamil are among the most extensively researched aryl acetonitrile-containing compounds used for the prevention and treatment of cancer and angina (Figure 1).[1] The selective *C*-monomethylation of these compounds leads to the synthesis of α-methylphenylacetonitriles (i.e. 2-arylproprionitriles), common building blocks for the construction of anti-inflammatory drugs such as ibuprofen, naproxen, and flurbiprofen.[3–5]

The replacement of a hydrogen atom (C–H) with a methyl group (C–Me) in bioactive compounds, known as the "Magic Methyl Effect" is highly valuable in medicinal chemistry, as this modification usually enhances the potency of lead compounds by altering their pharmacodynamic, pharmacokinetic, or conformational properties.[6–10] Studies on the structure-activity relationship (SAR) have shown that adding methyl groups to certain compounds significantly improve their IC_{50} values. For example, in the case of the anticancer drug tazemetostat, the incorporation of additional methyl groups in the development process resulted in a remarkable >100,000-fold enhancement in its potency.[8,11–13] However, late-stage methylation of complex bioactive molecules remains a significant challenge.[14,15] Achieving selective monomethylation is particularly difficult due to the frequent formation of dimethylated side products, the separation of which is rather laborious.[3,16,17] Traditional methylating agents, such as methyliodide, dimethylsulfate, or methyl fluorosulfonate pose significant toxicological concerns and health hazards.[16,18] Additionally, several organometallic reagents (e.g., methylboronic acid[19–22] and tetramethyltin),[23]

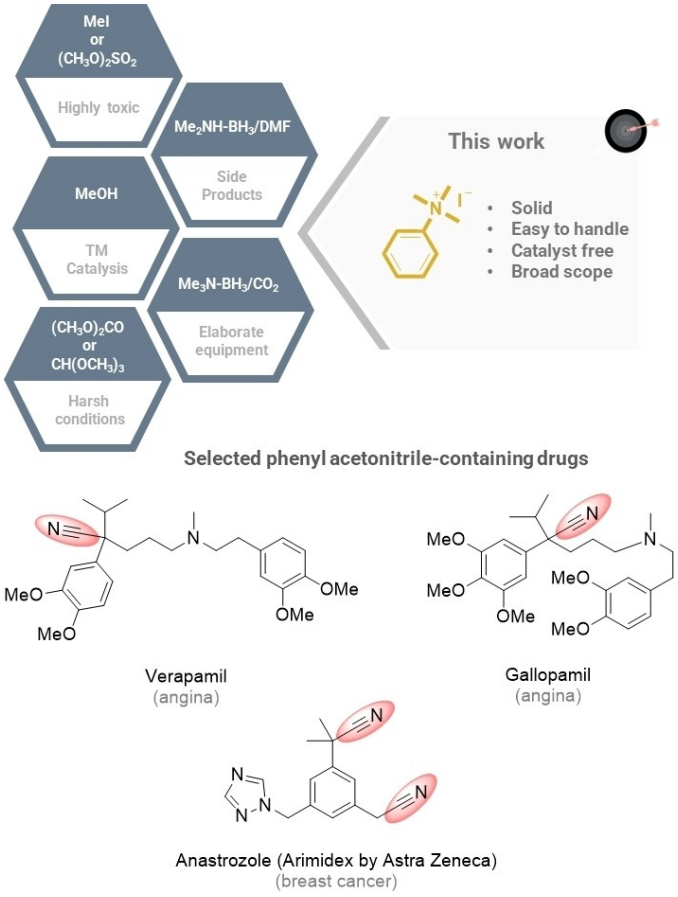

Figure 1. Strategies for the methylation of phenylacetonitriles (Top), and most prescribed nitrile-containing pharmaceuticals (Bottom).

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suffer from low functional group tolerance and unfavorable physical properties (low boiling points, air sensitivity), making them impractical to handle, especially on lab-scale syntheses.[24,25] Conventional late-stage methylation strategies often involve transition metal catalysis (C–H methylation), but these methods frequently require highly toxic reagents and solvents.[26] Dimethyl carbonate and trimethyl orthoformate have also been used for the methylation of phenylacetonitriles, however, harsh reaction conditions are required.[5,27] Wang *et al.* developed a Me_2NH-BH_3-mediated selective α-monomethylation protocol using *N*,*N*-dimethylformamide as the methyl source.[4] Nonetheless, the formation of side products cannot be excluded, complicating the purification process. Only one year later, Xi's group described a selective monomethylation protocol employing CO_2 as the methyl source in the presence of trimethylamine-borane, yet this method required elaborate high-pressure equipment.[28]

Previous studies within our group, have highlighted the potential of quaternary ammonium salts, as safer and non-carcinogenic alternative alkylating[29] and methylating agents in organic reactions.[30,31] These salts are known to function as surfactants,[32] ionic liquids,[32–35] and phase transfer materials.[33,36,37] They also exhibit stability in air and moisture, significantly enhancing their utility in both small- and large-scale reactions.[36,38,39]

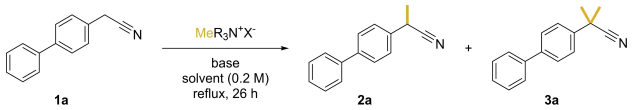
In light of the prevalence of the aryl acetonitrile moiety in various small-molecule drugs, there is a pressing need to develop advanced techniques for incorporating methyl groups, using safer reagents.[39] Therefore, this study aims to establish a selective and highly efficient metal-free protocol for the α-methylation of aryl acetonitriles by harnessing the remarkable properties of quaternary ammonium salts.

Results and Discussion

We started developing the methylation of (4-biphenyl)acetonitrile (**1 a**) based on conditions optimized in a previous study from our group, which focused on the methylation of aryl ketones with quaternary ammonium salts as methylating agents (Table 1, entry 1).[30] This initial experiment showed promising results, with ~15% of the substrate recovered, 59% converted to the monomethylated product **2 a**, and 13% to the dimethylated product **3 a**.

Next, we examined the impact and effectiveness of various bases. Cs_2CO_3 outperformed others, yielding 71% of the desired monomethylated product **2 a** (entry 2). In contrast, NaO*t*Bu favored dimethylated product **3 a** with a yield of 65% (entry 3) (see complete base screening list in the SI). With Cs_2CO_3 chosen as the preferred base, we further investigated the influence of the different quaternary ammonium salts. Similar reactivity was observed for $PhMe_3NBr$ and $PhMe_3NCl$, but the overall conversion was significantly lower compared to $PhMe_3NI$ in both cases (entries 4 and 5). Tetramethylammonium salts, bearing various counter ions were practically inefficient for our purposes (entries 6 and 7) (see complete quaternary ammonium salt screening list in the SI).

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent[c]	Base	Ammonium salt	1 a	Yield (%)[b] 2 a	3 a
1	toluene	KOH	$PhMe_3NI$	15	59	13
2	toluene	Cs_2CO_3	$PhMe_3NI$	11	71	13
3	toluene	NaO*t*Bu	$PhMe_3NI$	0	19	65
4	toluene	Cs_2CO_3	$PhMe_3NBr$	65	13	0
5	toluene	Cs_2CO_3	$PhMe_3NCl$	59	14	0
6	toluene	Cs_2CO_3	Me_4NBr	63	8	0
7	toluene	Cs_2CO_3	Me_4NF	20	43	0
8	*t*-BuOH	Cs_2CO_3	$PhMe_3NI$	7	68	19
9	Me-THF	Cs_2CO_3	$PhMe_3NI$	11	59	10
10	TFT	Cs_2CO_3	$PhMe_3NI$	6	68	16
11	toluene	Cs_2CO_3	MeI	24	38	2
12	toluene	Cs_2CO_3	Me_2SO_4	60	3	0

[a] Reactions were performed on a 0.6 mmol scale, with base (2 equiv.) and 2 equiv. of the respective ammonium salt under Ar atmosphere; reaction time 26 h, 120 °C. [b] Yields were determined by ^{1}H NMR spectroscopy using benzyl benzoate as internal standard. [c] reflux conditions.

To mitigate environmental impact, we tested the greener solvent alternatives *tert*-butanol (*t*-BuOH) and 2-methyl-THF (Me-THF) (Entries 8 and 9). Furthermore, trifluorotoluene (TFT) was included in the solvent screening as well (entry 10). Although similar yields and product ratios were obtained with these solvents, toluene was still superior and was selected for further substrate scope investigation (see complete solvent screening list in the SI). Finally, we determined the optimal reaction conditions to be $PhMe_3NI$ (2 equiv.) and Cs_2CO_3 (2 equiv.) in toluene (0.2 M) at 120 °C, achieving 71% yield of the desired 2-(4-biphenyl)propionitrile (**2 a**) after 26 h, as determined by ^{1}H NMR quantification (entry 2). Additionally, we compared the reactivity of $PhMe_3NI$ with that of MeI and Me_2SO_4 under otherwise identical conditions. Contrary to literature reports suggesting that dimethylation typically occurs with these reagents, our protocol did not exhibit such a behavior.[3] However, when MeI was used, a significantly lower yield of 38% of the monomethylated product was obtained (entry 11), while the use of Me_2SO_4 resulted in only negligible formation of the monomethylated product (entry 12).

After identifying the best performing conditions, we explored the substrate scope with respect to aryl acetonitriles (Scheme 1). A range of functional groups, including halides (products **2 h**--**2 n**) and ethers (products **2 e**--**2 g**), as well as heterocycles commonly found in bioactive compounds (products **2 o**–**2 q**), were tested regarding their ability to undergo monomethylation at the α-position. The desired compounds were obtained in isolated yields of up to 76%. In all cases,

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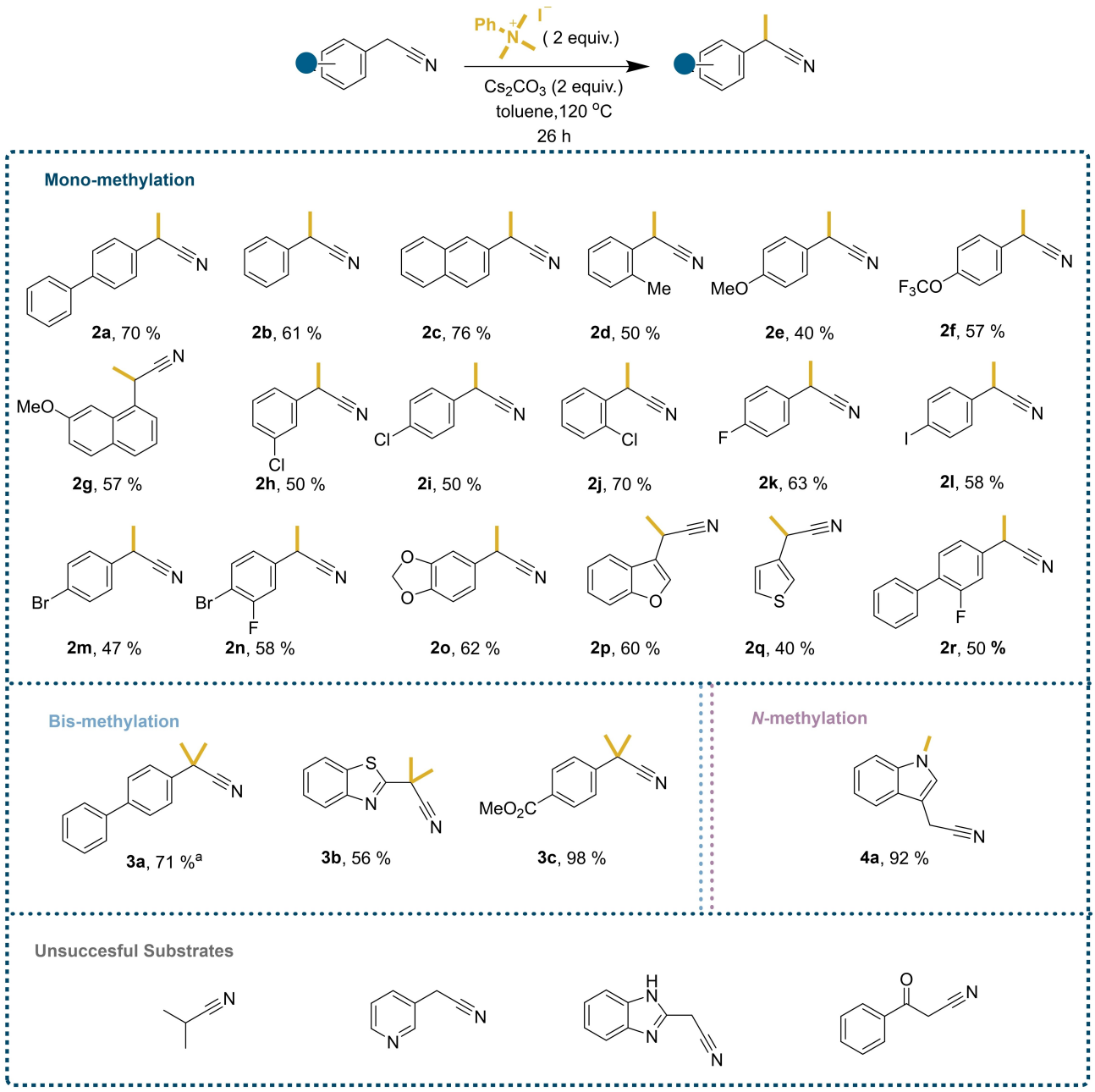


Scheme 1. Scope of a-methylation of phenylacetonitriles. [a] NaOtBu (2 equiv.) used as base.

stochiometric amounts of *N,N*-dimethylaniline were formed when using $PhMe_3NI$, which could be easily removed as its water-soluble HCl salt after a mild acidic workup.

The 2-(4-biphenyl)propionitrile (**2a**) used during the optimization process was isolated with a yield of 70%, demonstrating the method's efficiency. Additionally, the unsubstituted hydrocarbons 2-phenylpropionitrile (**2b**) and 2-(2-naphthyl)propionitrile (**2c**) were obtained with yields of 61% and 76%, respectively. A slightly lower yield of 50% was observed for 2-(2-methylphenyl)propionitrile (**2d**), likely due to the increased steric hindrance and the strong electron-donating effect of the methyl group in the *ortho*-position, which might reduce the availability of the α-hydrogens for deprotonation.

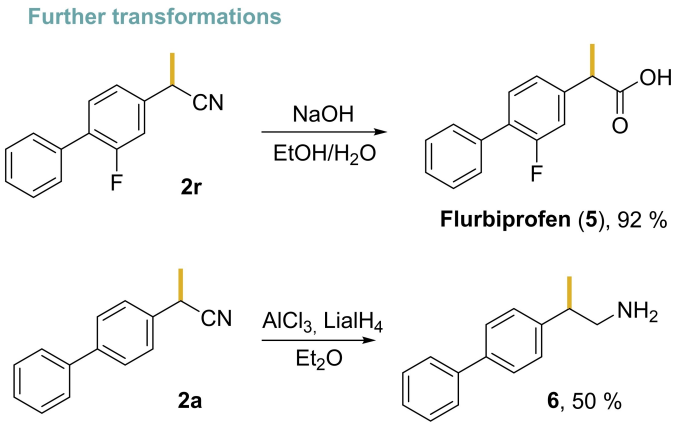
An even more profound electron-donating effect was observed in the case of 2-(4-methoxyphenyl)propionitrile (**2e**) (40% isolated yield). Although the optimal stoichiometry for the methylating agent was found to be 2 equivalents of the $PhMe_3NI$ in our previous optimization studies, 3 equivalents were needed in this case to enhance product formation. A moderate yield of 57% was achieved for 2-(4-(trifluoromethoxy)phenyl)propionitrile (**2f**), as well as for 2-(7-methoxynaphth-1-yl)propionitrile (**2g**). The reaction was also applicable to substrates bearing electron-withdrawing groups. The influence of the substitution pattern on the aromatic system was examined by methylating *meta*-, *ortho*-, and *para*-chlorine-substituted phenyl acetonitriles. Moderate yields of

50% were obtained for the 2-(3-chlorophenyl)propionitrile (**2h**) and 2-(4-chlorophenyl)propionitrile (**2i**). Despite the steric hindrance of the *ortho*-substituent, significantly higher product yield (70%) was achieved for the 2-(2-chlorophenyl)propionitrile (**2j**). Aryl acetonitriles bearing different halogens at the *para*-position were also tested, with the most electron-withdrawing fluoro derivative **2k** giving the highest yield of 63%. A slightly lower yield of 58% was obtained for 2-(4-iodophenyl)propionitrile (**2l**), and a moderate yield of 47% for the bromo-substituted equivalent **2m**. The di-halogenated compound **2n** was obtained with a 58% yield, presumably due to its stronger electron-withdrawing nature. It is worth mentioning that for electron-withdrawing substrates using fewer equivalents of the ammonium salts proved efficient to avoid possible overmethylation.

Our method is not limited to substituted aryl acetonitriles but can also be applied to heterocyclic substrates frequently found in bioactive molecules such as 1,3-benzodioxole, benzofuran, and thiophene. The respective monomethylated products were formed in good to moderate yields ranging from 40%–62% (products **2o–2q**). Additionally, we discovered that the bis-methylated product is selectively formed in the case of 2-(1,3-benzothiazol-2-yl)-2-methylpropionitrile (product **3b**). The presence of the benzothiazole ring probably increases the acidity of the benzylic position due to the stronger electron-withdrawing effect of both the nitrogen and the sulfur, resulting in selective dimethylation. More sensitive functional groups are well-tolerated, as demonstrated on the benzoate derivative. Using 3 equivalents of the ammonium salt, this derivative yielded the dimethylated product **3c** in a quantitative yield. With lower amounts of methylating agent, mixtures of mono- and demethylated product were obtained.

Furthermore, by adjusting the reaction parameters as outlined in the optimization table, the dimethylated biphenyl product **3a** can be selectively obtained using a different base, NaO*t*Bu. As expected, *N*-methylation occurred in the case of indole **4a**, however, despite further adjustments to the reaction parameters, we were unable to obtain any *C*-methylated product.[31]

Finally, we aimed to briefly showcase the utility of this protocol for late-stage methylation of bioactive molecules (Scheme 2). Using this method, we synthesized the precursor **2r** (50%), which, after subsequent hydrolysis, yielded the anti-inflammatory drug Flurbiprofen (**5**) quantitatively. Due to the versatility of the cyano group, we further proceeded with the modifications and successfully converted 2-(4-biphenyl)propionitrile (**2a**) to its respective amine **6**.



Scheme 2. Synthesis of Flurbiprofen and reduction of 2-(4-biphenyl)propionitrile (**2a**) to the corresponding amine.

Conclusions

In conclusion, we have presented a new protocol that employs quaternary ammonium salts as effective methylating agents for the selective α-C-monomethylation of (hetero)aryl acetonitriles, important precursors for the synthesis of key anti-inflammatory drugs. Selective dimethylation can be obtained by increasing the base strength. Our research paves the way for the exploration and utilization of quaternary ammonium salts in selectively methylating complex bioactive molecules, thereby expanding the toolkit for late-stage functionalization in medicinal chemistry, and ultimately contributing to the development of powerful pharmaceutical agents. In the future, we aim to expand the scope towards ethylation and benzylation reactions of arylacetonitriles, since in analogy to our previously reported **α**-ethylation and **α**-benzylation of aryl ketones.[30]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The original NMR-files are publicly available at the TU Wien data repository via following this DOI: 10.48436/bgazb-yz740.

Keywords: Magic methyl effect · Selective α-monomethylation · Phenylacetonitriles · Quaternary ammonium salts · Medicinal chemistry

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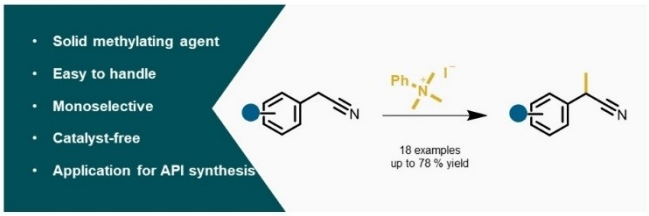

*E. Papaplioura, J. Templ, N. Wildhack, Prof. M. Schnürch**

Only one! Using a safe, easy to handle, and solid methylating agent, selective monomethylation of aryl acetonitriles is achieved. The method shows broad functional group tolerance and can be applied in the synthesis of active pharmaceutical ingredients potentially leading to compounds with increased biological activity due to the renowned magic methyl effect.