Organic LETTERS

Letter

pubs.acs.org/OrgLett

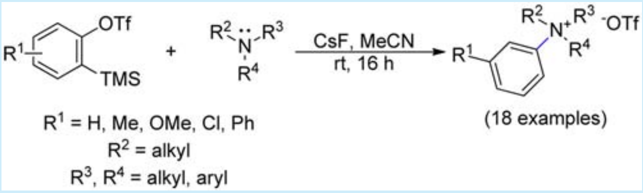
N-Arylation of Tertiary Amines under Mild Conditions

Maayan Hirsch,[†] Shubhendu Dhara,[†] and Charles E. Diesendruck*[,†]

[†]Schulich Faculty of Chemistry, Technion—Israel Institute of Technology, Haifa, Israel

Ⓢ *Supporting Information*

ABSTRACT: A transition-metal-free procedure for the *N*-arylation of tertiary amines to sp^3 quaternary ammonium salts is described. The presented conditions allow for the isolation of trialkylaryl, dialkyldiaryl, and novel triarylalkyl ammonium salts, including *N*-chiral quaternary ammonium salts. The reaction works at room temperature, open to air with electron-rich or -poor benzyne precursors and different tertiary amines, allowing the synthesis of a broad range of *N*-aryl ammonium salts that have applications in a variety of fields.



Quaternary ammonium salts are important industrial chemicals that are used as antimicrobials,[1] surfactants,[2] antistatic agents,[3] and more. In addition, these onium salts play a significant role as phase-transfer catalysts[4] and in anion-exchange membranes,[5] and constitute biologically relevant functional groups, playing essential roles in alkylation reactions[6] and in natural products.[7] In organic synthesis, quaternary ammonium salts are useful intermediates since they typically undergo secondary reactions such as Hoffman elimination,[8] dealkylation,[9] and Aza–Claisen rearrangement,[10] leading to the construction of relevant anilines.[11] Notably, elimination and demethylation are the main pathway in the decomposition of anion exchange membranes, an important application that still cannot meet industrial requirements for the development of efficient alkali fuel cells.[5a] Given the importance of this functional group in different fields, it is surprising that multiarylated ammonium salts are rarely found. A tetra-aryl ammonium salt should be quite stable toward Hoffman elimination, since the elimination product is a high-energy benzyne. To study the effects additional aryl substituents have on the stability of these salts, as well as in other applications, a general methodology allowing for the *N*-arylation of tertiary amines is required.

The alkylation of most tertiary amines by nucleophilic substitution is easily achievable using the Menshutkin reaction;[12] however, triaryl amines are not easily alkylated due to their low nucleophilicity. Further, sp^2 carbons (including aryl groups) are mostly unreactive toward tertiary amine nucleophiles. Heterocycles can arylate trialkyl amines, especially nonsterically crowded ones, but under the reaction conditions these tend to undergo dealkylation.[13] Recently, Gao and co-workers have shown that *N*-heterocycles can be arylated under harsh conditions;[14] however, this reaction only works when the product is a stabilized sp^2 nitrogen.

The arylation of tertiary anilines is even more challenging. Aryl substituents reduce the nucleophilicity of amines both by electronic and steric effects. That said, a few specific *N*-arylations of *N*-substituted anilines were previously described using strong electrophiles. Intramolecular arylation of tertiary anilines was accomplished by heating a diazonium salt to form an ammonium carbazole;[15] however, no examples for intermolecular reactions were provided. In a more peculiar example, Shchepina et al. investigated the β-decay of hexatritium benzene to produce a phenyl cation, which reacted in situ with triphenylamine.[16] This resulted in low yields of isotopically labeled $C_6T_5(C_6H_5)_3N^+\ I^-$, as well as several other byproducts.[16] With these specific examples in mind, we decided to develop a general, simple approach for the *N*-arylation of tertiary anilines, capable of producing tetrasubstituted ammonium salts with a variety of alkyl and aryl substituents. Given the difficulties in cleanly producing singlet phenyl cations and their low selectivity, we decided to experiment with a different strong aryl electrophile. To that end, we decided to use benzyne precursors, given that pyramidalization of the sp-hybridized carbons of benzynes leads to strong electrophilicity.[17] A few examples of nucleophilic attacks of benzyne by tertiary amines are found in the literature,[11a,b,18] but in all cases the quartenarized ammonium salt was either a byproduct or underwent a secondary reaction, as described above.

2-(Trimethylsilyl)phenyl triflate and its derivatives (**1**) have been extensively used as benzyne precursors, for example in the arylation of sulfonamides, phenols, carboxylic acids, and aldehydes,[11c,19] as well as primary, secondary amines, and imidazoles.[11c,d,20] Hence we chose **1a** as the benzyne precursor for developing our reaction with different tertiary amine nucleophiles (Table 1). **1a** in MeCN was added to a mixture of CsF (to generate the benzyne intermediate) and the nucleophile (tertiary amine) at room temperature open to air. Reaction of **1a** with *N*,*N*-dimethylaniline (**2b**) worked well in our hands,[18] providing the desired *N*,*N*-dimethyl-*N*-phenylanilinium triflate (**3b**) in good yield (Table 1, entry 3). NMR and high-resolution mass spectrometry pointed to the desired product and X-ray diffraction of single crystals of the product further

Received: January 10, 2016
Published: February 23, 2016

DOI: 10.1021/acs.orglett.6b00078
Org. Lett. 2016, 18, 980−983

Table 1. *N*-Phenylation of Tertiary Amines with Different Number of Alkyl and Aryl Substituents[a]

entry	amine	R^2	R^3	R^4	product	yield [%][b]
1	**2a**	Et	Et	Et	**3a**	0
2[c]	**2a**	Et	Et	Et	**3a**	78
3	**2b**	Me	Me	Ph	**3b**	86
4	**2c**	Me	Ph	Ph	**3c**	61
5	**2d**	Ph	Ph	Ph	**3d**	0
6	**2e**	Tol	Tol	Tol	**3e**	0

[a] General conditions: **1a** (2.5 equiv), **2** (1.0 equiv), CsF (5.0 equiv), MeCN (5 mL), rt, and 16 h. [b] Isolated yields. [c] Reaction was run in MeCN:MeOH (9:1) (5 mL).

demonstrated the isolation of a stable quaternary ammonium salt (see the Supporting Information).

With a change in the number of alkyl and aryl substituents, tertiary amines with varied nucleophilicity were tested (**2a**,**c**–**e**) (Table 1, entries 1, 2, 4–6). Trialkylamines such as triethylamine (**2a**), which are the most nucleophilic, provided no desired product under our initial reaction conditions. Analysis of the reaction products indicated the presence of significant amounts of *N*,*N*-diethylaniline, which suggests that the desired product was initially obtained but underwent the typically observed Hoffman elimination.[21] The analysis excluded Stevens rearrangement.[22] Following the proposed reaction mechanism (Scheme 1), a highly basic zwitterionic intermediate is formed that could cause the undesired elimination. To solve this problem, MeOH was added to the reaction solvent to include a proton source (Table 1, entry 2). In this case, under mild conditions, the desired ammonium salt **3a** was obtained in good yield.

Next, we tested *N*-methyl-*N*-phenylaniline (**2c**) as a less nucleophilic substrate. This reactant still provided the desired ammonium salt **3c** with reasonable yield (Table 1, entry 4). Finally, the highly desirable triarylamines were tested. The phenylation of triphenyl amine would produce tetraphenyl ammonium triflate, a simple molecule that has not yet been prepared. However, triphenyl amine provided no product under the regular reaction conditions (Table 1, entry 5). We changed reaction conditions to try to induce the reaction—running a neat reaction in molten triphenyl amine, changing temperature and fluoride source, adding a proton source—but no product was obtained. Tri-*p*-tolylamine also did not provide any product under any reaction conditions (Table 1, entry 6).

Having studied the effect aryl substituents have on the tertiary amine nucleophiles, we went on to study the scope of this reaction by looking at different substituents in the benzyne precursors. Under the same reaction conditions, using **2b** as a model tertiary amine, we tested benzyne precursors with substituents at the 3 or 6 positions (**1b**–**d**). These provided a clean reaction, producing a single quaternary ammonium product with the substituent at the meta position (**3f**–**h**) (Table 2, entries 2–4). When triflates had a substituent at the 4 position (**1e**), the reaction provided a mixture of isomeric products, with the substituent either in the *meta* or *para* position (**3h**,**i**) in a ca. 1:1 ratio according to NMR (Table 2, entry 5). In terms of electronic effects, electron-donating groups such as

Scheme 1. Proposed Mechanism

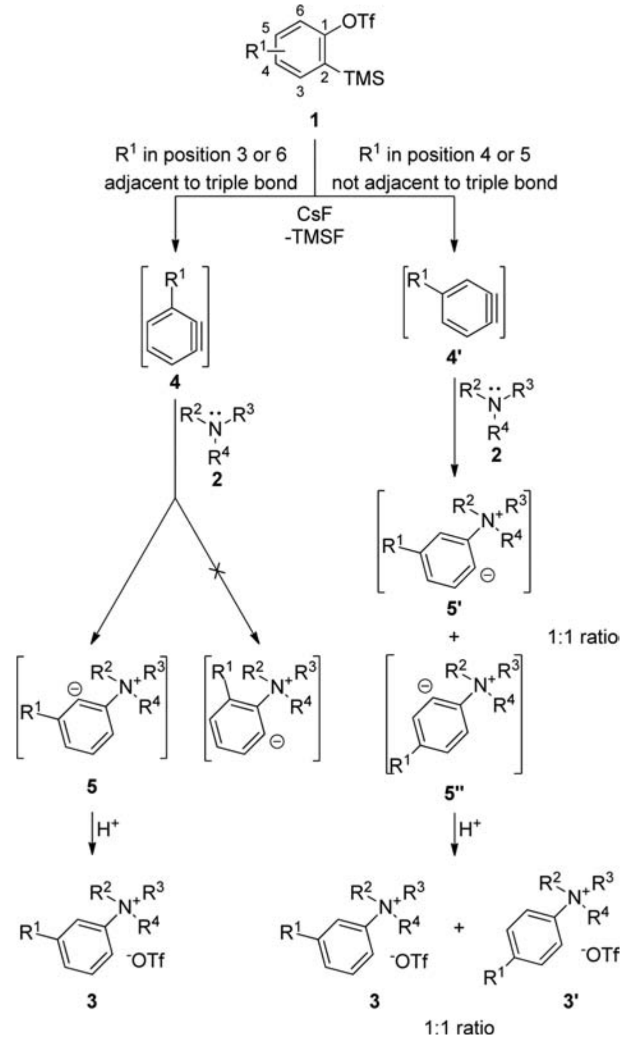
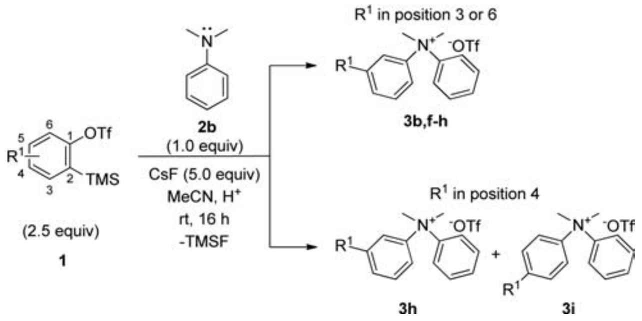


Table 2. *N*-Arylation of *N*,*N*-Dimethylaniline with Substituted Aryls[a]

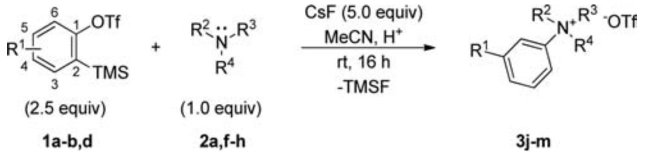


entry	benzyne precursor	R^1 (position)	product	yield [%][b]
1	**1a**	H	**3b**	86
2	**1b**	OMe (3)	**3f**	95
3	**1c**	Cl (6)	**3g**	76
4	**1d**	Me (6)	**3h**	97
5	**1e**	Me (4)	**3h+3i (1:1)**	89
6	**1f**	Ph (5,6)	**3j**	80

[a] General conditions: **1** (2.5 equiv), **2b** (1.0 equiv), CsF (5.0 equiv), MeCN (5 mL), rt, and 16 h. [b] Isolated yields.

DOI: 10.1021/acs.orglett.6b00078
Org. Lett. 2016, 18, 980–983

Table 3. Additional Examples of *N*-Arylations of Tertiary Amines[a]



entry	benzyne precursor	R^1 (pos.)	amine	R^2, R^3, R^4	prod.	yield [%][b]
1[c]	**1d**	Me (6)	**2a**	Et, Et, Et	**3k**	89
2	**1a**	H	**2f**	*n*-Bu, *n*-Bu, *n*-Bu	**3l**	quant
3	**1a**	H	**2g**	Et, Et, Ph	**3m**	quant
4	**1g**	Ph (4, 5)	**2b**	Me, Me, Ph	**3j**	67
5	**1b**	OMe (3)	**2c**	Me, Ph, Ph	**3n**	92
6	**1b**	Me (6)	**2c**	Me, Ph, Ph	**3o**	19
7	**1b**	Me (4)	**2c**	Me, Ph, Ph	**3o**+**3p** (1:1)	quant
8	**1b**	OMe (3)	**2h**	Me, Ph, 3-Tol	**3q**	40
9	**1b**	OMe (3)	**2i**	*n*-Bu, Ph, 3-Tol	**3r**	8

[a] General conditions: **1** (2.5 equiv), **2** (1.0 equiv), CsF (5.0 equiv), MeCN (5 mL), rt, and 16 h. [b] Isolated yields. [c] Reaction was run in MeCN/MeOH (9:1) (5 mL).

methoxy and methyl (**1b**,**d**,**e**) improved reaction yield (Table 2, entries 2, 4–5), while electron-withdrawing substituents such as a chloride or using a naphthyl triflate (**1c**, **1f**) decreased slightly the isolated yields (Table 2, entries 3, 6).

The reaction mechanism follows the typical pathway for benzyne chemistry. First, the fluoride induces desilylative elimination of triflate from 2-(trimethylsilyl)phenyl triflate (**1**) to provide an aryne intermediate (**4**).[23] The benzyne undergoes nucleophilic attack by the tertiary amine, providing an intermediate zwitterion (**5**), which abstracts a proton from the reaction medium to yield the desired quaternary salt (**3**). The regioselectivity in nucleophilic attack on benzynes is typically dictated by electronic and steric effects of the substituents. Arynes with electron donating substituents adjacent to the triple bond typically show regioselective attack at *meta* due to the electrophilicity of that carbon caused by inductive effects (Table 2, entries 2, 4). In the case of strong electron withdrawing groups, electronic effects overcome steric effects to give a greater *ortho*/*meta* ratio.[24] In our study, steric effects predominated over electronic effects, probably owing to poor nucleophilicity of the reactants (Table 2, entries 3, 6).[25] Both electron donating groups (Table 2, entries 2, 4) and electron withdrawing groups (Table 2, entries 3, 6) provided *meta* regioselectivity. If the substituents are not adjacent to the triple bond, the electronic effects are negligible on the regioselectivity of the incoming nucleophile,[24] providing both products in a close to 1:1 ratio (Table 2, entry 5).

Finally, we decided to increase the scope of the reaction combining different tertiary amines and benzyne precursors (Table 3). Isolated yields of quaternary ammonium salts followed the expected from previously described experiments. An interesting perspective to this reaction was to produce *N*-chiral acyclic ammonium salts, which can have important implications in the field of asymmetric phase-transfer catalysis (APTC).[26] We prepared two prochiral alkyldiarylamines (**2h**–**i**) by the alkylation of 3-methyl-*N*-phenylaniline and subjected them to our reaction conditions using **1b** as benzyne precursor (Table 3, entries 8–9). While the isolated yields were below the expected, our reaction produced racemic mixtures of the desired *N*-chiral quaternary ammonium salts **3q** and **3r**. These are the first examples of *N*-chiral ammonium salts with large aryl substituents that, like their cyclic peers, may be useful in APTC. Further studies on their separation and applications are ongoing in our laboratory.

To conclude, we have developed an efficient, mild, transition-metal-free method for the *N*-arylation of tertiary amines to sp^3 quaternary ammonium salts. The regioselectivity of non-substituted and monosubstituted 2-(trimethylsilyl)phenyl triflate in positions 3 or 6 is complete, producing *meta* substituted aryl ammonium salts. Triflates with electron donating groups afford the desired salts in higher yields, whereas triflates with electron withdrawing groups decrease the isolated yields slightly. The reaction scope is quite large, allowing for arylation of tertiary amines containing up to two aryl substituents. This reaction enabled the first mild synthesis of quaternary ammonium salts containing three aryl substituents in high yields. Further, we have demonstrated the potential of this reaction in producing new acyclic *N*-chiral quaternary ammonium salts with several aryl substituents, which, after resolution, may have useful applications in APTC.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00078.

Experimental procedures and characterization of new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: charles@tx.technion.ac.il

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Technion Start-up Grant. S.D. is grateful to the Schulich Foundation for a postdoctoral fellowship. C.E.D. is grateful to the American Technion Society for a Women's Division Career Advancement Chair.

REFERENCES

(1) (a) Muñoz-Bonilla, A.; Fernández-Garcia, M. *Prog. Polym. Sci.* **2012**, *37*, 281−339. (b) Jennings, M. C.; Minbiole, K. P. C.; Wuest, W. M. *ACS Infect. Dis.* **2015**, *1*, 288−303.

(2) (a) Branzoi, V.; Branzoi, F.; Baibarac, M. *Mater. Chem. Phys.* **2000**, *65*, 288−297. (b) Fuchs-Godec, R. *Colloids Surf., A* **2006**, *280*, 130−139.

(3) (a) Hong, J. W.; Kim, H. K.; Yu, J. a.; Kim, Y. B. *J. Appl. Polym. Sci.* **2002**, *84*, 132−137. (b) Kuang, M.; Shiyi, Z.; Lei, J.; Li, Q. *J. Appl. Polym. Sci.* **2008**, *109*, 3887−3891.

(4) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415.

(5) (a) Varcoe, J. R.; Atanassov, P.; Dekel, D. R.; Herring, A. M.; Hickner, M. A.; Kohl, P. A.; Kucernak, A. R.; Mustain, W. E.; Nijmeijer, K.; Scott, K.; Xu, T.; Zhuang, L. *Energy Environ. Sci.* **2014**, *7*, 3135−3191. (b) Varcoe, J. R.; Slade, R. C. T. *Fuel Cells* **2005**, *5*, 187−200.

(6) Liang, G.; Encell, L.; Nelson, M. G.; Switzer, C.; Shuker, D. E. G.; Gold, B. *J. Am. Chem. Soc.* **1995**, *117*, 10135−10136.

(7) (a) Rochfort, S. J.; Towerzey, L.; Carroll, A.; King, G.; Michael, A.; Pierens, G.; Rali, T.; Redburn, J.; Whitmore, J.; Quinn, R. J. *J. Nat. Prod.* **2005**, *68*, 1080−1082. (b) Martin, F.; Grkovic, T.; Sykes, M. L.; Shelper, T.; Avery, V. M.; Camp, D.; Quinn, R. J.; Davis, R. a. *J. Nat. Prod.* **2011**, *74*, 2425−2430. (c) Jiménez, C.; Crews, P. *Tetrahedron* **1991**, *47*, 2097−2102. (d) Leboeuf, M.; Cave, A.; Ranaivo, A. *Can. J. Chem.* **1989**, *67*, 947−952.

(8) (a) Sato, Y.; Aoyama, T.; Shirai, H. *J. Organomet. Chem.* **1974**, *82*, 21−27. (b) Karmakar, R.; Yun, S. Y.; Wang, K. P.; Lee, D. *Org. Lett.* **2014**, *16*, 6−9.

(9) (a) Lepley, A. R.; Becker, R. H.; Giumanni, A. G. *J. Org. Chem.* **1971**, *36*, 1222−1227. (b) Pine, S. H. *Org. React.* **1970**, *18*, 403−464.

(10) Cant, A. A.; Bertrand, G. H. V; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199−5202.

(11) (a) Bhojgude, S. S.; Kaicharla, T.; Biju, A. T. *Org. Lett.* **2013**, *15*, 5452−4455. (b) Varlamov, A. V.; Guranova, N. I.; Borisova, T. N.; Toze, F. a. a.; Ovcharov, M. V.; Kristancho, S.; Voskressensky, L. G. *Tetrahedron* **2015**, *71*, 1175−1181. (c) Liu, Z.; Larock, R. *J. Org. Chem.* **2006**, *71*, 3198−3209. (d) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673−4675.

(12) Menschutkin, N. Z. *Phys. Chem.* **1890**, *6*, 41−57.

(13) (a) Olberg, D. E.; Arukwe, J. M.; Grace, D.; Hjelstuen, O. K.; Solbakken, M.; Kindberg, G. M. *J. Med. Chem.* **2010**, *53*, 1732−1740. (b) Kunishima, M.; Ujigawa, T.; Nagaoka, Y.; Kawachi, C.; Hioki, K.; Shiro, M. *Chem. - Eur. J.* **2012**, *18*, 15856−15867. (c) Xiong, H.; Hoye, A. T.; Fan, K.-H.; Li, X.; Clemens, J.; Horchler, C. L.; Lim, N. C.; Attardo, G. *Org. Lett.* **2015**, *17*, 3726−3729.

(14) (a) Lv, T.; Wang, Z.; You, J.; Lan, J.; Gao, G. *J. Org. Chem.* **2013**, *78*, 5723−5730. (b) Li, S.; Yang, F.; Lv, T.; Lan, J.; Gao, G.; You, J. *Chem. Commun.* **2014**, *50*, 3941−3943.

(15) Hellwinkel, D.; Seifert, H. *Chem. Ber.* **1972**, *105*, 880−906.

(16) Shchepina, N. E.; Nefedov, V. D.; Toropova, M. a.; Avrorin, V. V.; Lewis, S. B.; Mattson, B. *Tetrahedron Lett.* **2000**, *41*, 5303−5306.

(17) (a) Diesendruck, C. E.; Zhu, L.; Moore, J. S. *Chem. Commun.* **2014**, *50*, 13235−13238. (b) Maier, W. F.; Lau, G. C.; McEwen, A. B. *J. Am. Chem. Soc.* **1985**, *107*, 4724−4731.

(18) Okuma, K.; Nojima, A.; Nakamura, Y.; Matsunaga, N.; Nagahora, N.; Shioji, K. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 328−332.

(19) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761−9764.

(20) Yoshida, H.; Sugiura, S.; Kunai, A. *Org. Lett.* **2002**, *4*, 2767−2769.

(21) (a) Giumanini, A. G. *J. Org. Chem.* **1972**, *37*, 513−514. (b) Sato, Y.; Ban, Y.; Aoyama, T.; Shirai, H. *J. Org. Chem.* **1976**, *41*, 1962−1965.

(22) *Comprehensive Organic Name Reactions and Reagents*; Wang, Z., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2010; pp 2668−2672.

(23) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211−1214.

(24) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Elsevier Science Ltd.: Amsterdam, Netherlands, 1991; Vol. 4, pp 483−515.

(25) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, a. *J. Org. Chem.* **2001**, *66*, 1403−1412.

(26) Tan, J.; Yasuda, N. *Org. Process Res. Dev.* **2015**, *19*, 1731−1746.