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Thermally generated phenylcarbenium ions: acid-free and self-quenching Friedel–Crafts reactions

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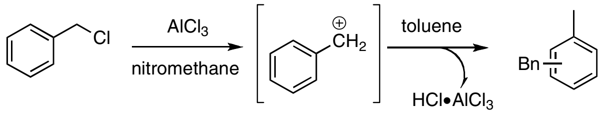
Abstract—2-Benzyloxy-1-methylpyridinium triflate (**1**) serves as a stable precursor to a phenylcarbenium species as evidenced by its reactivity in Friedel–Crafts alkylations with electron-rich arenes.

The recognized importance of carbocations in organic chemistry[1] dates back to when Ingold and Hughes first described them as intermediates in the S_N1 reaction.[2,3] Carbocations play a crucial role in many important reactions including Friedel–Crafts alkylations (e.g., Scheme 1) and acylations,[4] Prins reactions,[5] pinacol rearrangements,[6] Nazarov cyclizations,[7] Ritter reactions,[8] Mukaiyama aldol couplings,[9] and others.

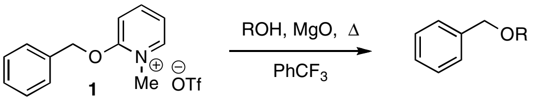
Carbocations are frequently used to facilitate key steps in natural products synthesis. For example, Johnson's synthesis of progesterone features an elegant cascade cation–π cyclization to assemble the steroid core.[10,11] Modern synthetic approaches to the 'ladder' polycyclic polyethers focus on conceptually related cascade cation–epoxide cyclizations.[12–14] Such studies require means of generating cation initiators to trigger cyclization under conditions that is compatible with the rest of the molecule.

For synthetic purposes, carbenium ions (trivalent carbocations) are typically generated from aldehydes, alcohols, olefins, and alkyl halides using strong activators like Lewis or protic acids.[15] Olah contributed significantly to this field with his development of 'superacid' solvents,[16] which make it possible to prepare free carbocations that are too reactive to exist in less acidic media.[17] In general, however, the need for acidic media limits the range of functional groups that are compatible with traditional methods for generating reactive carbenium species.



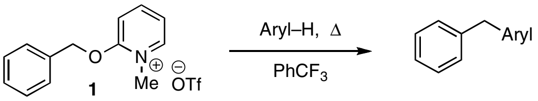
Scheme 1. Lewis acid-promoted carbocation formation with accompanying Friedel–Crafts alkylation.[4]

Alternatively, newer methods involving thermal decomposition of *N*-alkyl, *N*-nitrosamides[18] or photolysis of diazonium salts[19–21] circumvent the need for strong acid activators, but these methods require the use of dangerous or unstable starting materials. Furthermore, the reaction of a cation with a neutral arene nucleophile generates a strongly acidic by-product (e.g., $HAlCl_4$, Scheme 1).



(1)

Our group recently reported the synthesis of benzyl ethers via thermolysis of 2-benzyloxy-1-methylpyridinium triflate (**1**)[22] in the presence of alcohols (Eq. 1).[23] We postulated an S_N1-type mechanism proceeding through a phenylcarbenium triflate salt.



(2)

Given the broader importance of generating reactive intermediates under neutral conditions, our new study

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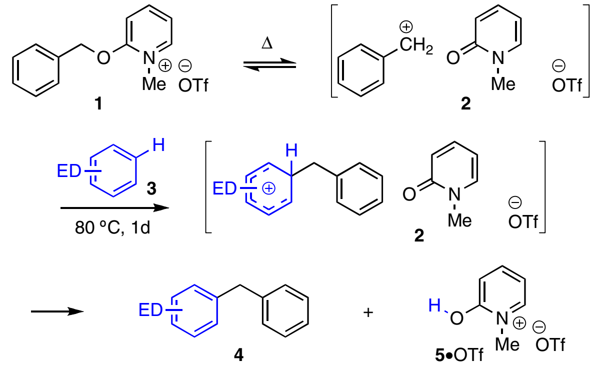


Scheme 2. Proposed mechanism of the Friedel–Crafts reaction of **1** with electron-rich arenes.

aims to determine if **1** indeed serves as a stable, pre-activated source of phenylcarbenium by exploring Friedel–Crafts benzylation reactions[24] under conditions that do not involve the addition of acid or other activating agent (Eq. 2).

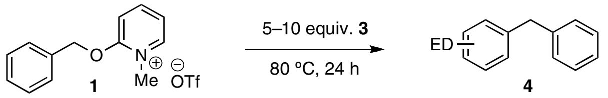
Herein we report data and observations on the thermolysis of **1** in the presence of various arenes, which in most cases afforded characterizable Friedel–Crafts-type products.[25]

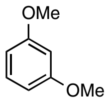
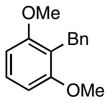
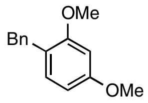
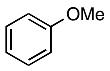
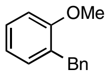
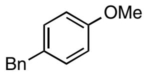
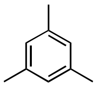
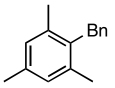
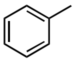
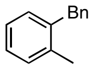
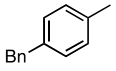
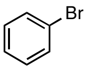
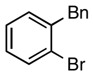
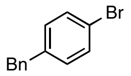
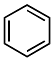
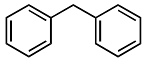
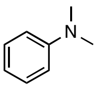
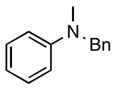
The mechanistic rationale is outlined in Scheme 2: thermolysis of **1** was expected to release the benzyl electrophile transiently along with pyridone **2**. Then, the reaction of an arene substrate with phenylcarbenium would furnish **4**. The strong acid by-product (in this case, triflic acid) would be buffered by pyridone **2** through the formation of **5**. Note that the hydroxypyridinium species (**5**) is 10 or more orders of magnitude less acidic than triflic acid: pK_a (TfOH) = −10 to −15,[26] whereas pK_a (**5**) = 0.30.[27]

Electron-rich arenes such as anisole or 1,3-dimethoxybenzene efficiently trapped the putative phenylcarbenium species to provide the corresponding diarylmethanes in excellent yields (Table 1), whether the reaction is conducted neat or in an inert aromatic solvent (cf. entry 2). As indicated in entry 2, *productive Friedel–Crafts reactions occur even under non-acidic conditions* (i.e., buffered with magnesium oxide). Less activated arene substrates provided more modest yields (entries 5–8).

Interestingly, the reaction between **1** and *N*,*N*-dimethylaniline took a different course: one of the methyl groups was replaced with a benzyl group to yield *N*-benzyl, *N*-methylaniline (entry 9).[28] We draw an analogy between the *N*-methyl→benzyl exchange that we observed (entry

Table 1. Reaction of **1** with electron-rich arenes[25]



Entry	Arene 5	Isolated products	Yield[a] (ratio)[b]
1		: 	100 (12:88)
2		: 	93, 94[c], 90[d] (65:35)
3			57
4		: 	72 (38:62)
5		: 	72 (33:67)
6			43
7			65

[a] Yields refer to isolated product judged to be >95% pure by ^{1}H NMR spectroscopy. All compounds provided characterization data in accord with the literature reports.

[b] Regioisomer ratios estimated by ^{1}H NMR.[31]

[c] Magnesium oxide (MgO, 1.0 equiv) added as the terminal acid scavenger.

[d] Reaction conducted in trifluorotoluene ($PhCF_3$, 1.0 mL/mmol of **1**) as solvent; MgO (1.0 equiv) added as the terminal acid scavenger.

9) and the *O*-methyl→benzyl exchange detailed by Speranza and co-workers.[29] Other labs have reported similar but less dramatic observations of heteroatom substitution products under conventional Friedel–Crafts conditions.[30]

Based on these results, we conclude that a reactive benzyl electrophile is generated upon mild thermal activation (ca. 80 °C) of **1**. Benzyloxypyridinium triflate **1** is unique among phenylcarbenium precursors: it is neutral, pre-activated, stable at room temperature, and can be stored and handled without special precautions. The reactive electrophilic species is produced alongside *N*-methyl-pyridone (**2**), which can act as an acid scavenger (**2**→**5**) to moderate the acidity of the reaction.

In summary, 2-benzyloxy-1-methylpyridinium triflate (**1**) decomposes upon heating to release a phenylcarbenium species, as evidenced by its efficient Friedel–Crafts alkylations of electron-rich arenes.[32] These reactions do not require strong Lewis or protic acids, in contrast to the classical conditions for Friedel–Crafts reactions, and can even be conducted in the presence of heterogeneous base (MgO). Stable species that produce carbocations under mild, neutral conditions contribute to the study of reactive intermediates in organic chemistry and their potential applications in synthesis.

Acknowledgments

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25. *General procedure:* An oven-dried vial with magnetic stirbar was charged with arene **3** (5–10 mol equiv) and pyridinium triflate **1** (0.5 mmol, 1 mol equiv). The vial was heated at 80 °C for 24 h. The reaction mixture was diluted with 49:1 hexanes/EtOAc (10 mL) and filtered over a bed of Celite. Solvent and excess arene were removed in vacuo to yield the diarylmethane product. When necessary, the product was further purified by silica gel chromatography. All compounds were judged to be >95% pure by ^{1}H NMR spectroscopy and provided characterization data in accord with the literature reports.
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29. By exploiting the nuclear decay of tri-tritiated toluene (PhC(^{3}H)$_3$; $^{3}\mathrm{H}\rightarrow{}^{3}\mathrm{He}^{+} + \mathrm{e}^{-}$), Speranza and coworkers showed that under certain conditions the major product of the reaction between 2,6-dimethylanisole and phenylcarbenium-t_2 (PhC(^{3}H)$_2$$^{+}$) was benzyl 2,6-dimethylphenyl ether. See: Anglini, G.; Sparapani, C.; Speranza, M. *Gazz. Chim. Ital.* **1986**, *116*, 479.
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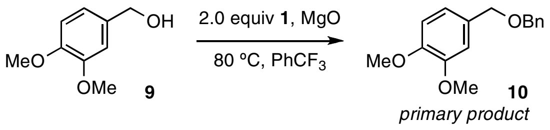
P. *J. Org. Chem.* **1982**, *47*, 5204; (c) Laali, K. *J. Org. Chem.* **1985**, *50*, 3638.

31. Friedel–Crafts alkylations of electron-rich arenes are thought to have early transition states with little σ-bond character between the electrophile and arene. Therefore, the *o*/*p* selectivity is generally modest. Less activated arene substrates react through later transition states, which usually translate to higher *para*-selectivity (cf. entries 2 and 6). For further discussion, see: (a) March, J.; Smith, M. B. *Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 6th ed.; Wiley and Sons: Hoboken: NJ, 2007, pp 670–671; (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanism*, 4th ed.; Kluwer Academic/Plenum: New York, 2000, pp 551–583.
32. With respect to our earlier reports on the use of **1** as a neutral reagent for the synthesis of benzyl ethers,[23a,b] note that the formation of benzyl ether takes precedence over Friedel–Crafts chemistry.



9

10

primary product