



Efficient functionalization of quinolizinium cations with organotrifluoroborates in water

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ABSTRACT

An efficient functionalization of the quinolizinium system is reported. The reaction of the four isomeric bromoquinolizinium salts with different organotrifluoroborates afforded alkyl-, vinyl-, aryl-, and heteroaryl quinolizinium derivatives in moderate or good yields. Reactions are carried out in water using a counterion exchange for the isolation of the cationic-coupled compounds.

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Since the discovery of the use of organic molecules for the generation of optical second harmonics (SHG) by Rentzepis and Heilmeyer,¹ one of the main objectives in the development of materials for nonlinear optical applications is the search for highly active chromophores with large second-order polarizabilities. The majority of chromophores studied to date, whether metal-containing or purely organic, contain an electron-donor group (D) connected to an electron acceptor (A) through a polarizable π -conjugated bridge. Thus, a variety of donor–acceptor organic molecules containing different acceptors have been reported.²

The use of charge acceptors in D– π –A NLO-phores has barely been explored to date, with pyridinium salts being the most widely studied acceptors in this context.³ Specifically, several studies on *trans*-4'-(dimethylamino)-N-methyl-4-stilbazolium tosylate (DAST) have been reported^{3a,4} (Fig. 1).

Recently, we carried out a study, in which different azinium (pyridinium, quinolinium, and isoquinolinium), azolium (imidazolium and benzimidazolium), and azonia (quinolizinium and azaquinolizinium) cations were compared as potential acceptor units in a variety of NLO-catiophores. Initial results proved that azonia salts⁵ act as the most powerful cationic acceptors, conferring on different types of *push–pull* charged chromophores the largest second-order polarizabilities (β).⁶ However, the synthesis and functionalization of the quinolizinium and related heteroaromatic cations still remain relatively unexplored, a situation that results

in low availability of quinolizinium-type derivatives for NLO studies.

Although we have made significant contributions in this field through the application of palladium-catalyzed⁷ and metathesis reactions⁸ to azonia cations, the functionalization of quinolizinium-type cations still suffers from limitations, particularly for some of the four possible positions in this heterocyclic system. We report here an improved and greener procedure that will allow straightforward and efficient access to charged chromophores based on quinolizinium-type cations as acceptor units.

Previous comparative studies from our laboratory showed that the Stille coupling reaction was the most efficient procedure in comparison to other palladium-catalyzed cross-coupling reactions such as the Suzuki and Negishi reactions to produce moderate (in most cases) or high yields of some aryl-, heteroaryl-, and alkynyl-substituted quinolizinium cations.^{7c}

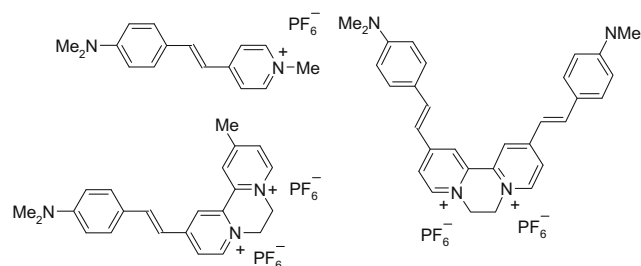


Figure 1. Examples of D– π –A NLO-phores based on pyridinium acceptor units.

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However, we were unable to achieve the coupling reaction with stannanes bearing Csp^3 -hybridized substituents, and the reaction of tributylvinylstannane failed to give the 4-vinyl-quinolizinium and gave low yields (10–22%) of the 2- and 3-isomers. The need for a more efficient procedure for the preparation of different quinolizinium derivatives led us to re-investigate the Suzuki–Miyaura reaction using alternative organoborons as coupling partners and specifically potassium organotrifluoroborates.^{9,10}

Initially, the reaction of the potassium phenyltrifluoroborate and 2-bromoquinolizinium bromide (**2**) was attempted in order to optimise the reaction conditions in terms of catalysts, ligands, bases, and solvents. Our first choices were the optimized conditions used in the Suzuki coupling reaction between **2** and phenylboronic acid^{7c} (Table 1, entry 1). However, under these conditions, the reaction did not proceed, with most of the starting quinolizinium salt recovered after 24 h.

Similar results were obtained either by heating the reaction at 80 °C or by using biphenyl*tert*butylphosphine as an alternative ligand, although in both cases traces of the coupling product were detected. Other conditions commonly employed in the reaction of potassium aryltrifluoroborates and electron-poor aryl halides were also tested.^{9d,e} The results are summarized in Table 1, and entries 4 and 5 show that when the reaction was carried out under ligandless conditions in the presence of $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ and Et_3N (or Hünig's base) in ethanol or methanol as solvent, extensive decomposition occurred. Surprisingly, the reaction carried out in the presence of $\text{Pd}(\text{OAc})_2$ and K_2CO_3 in $\text{EtOH}/\text{H}_2\text{O}$ (1:1) led to 4-ethoxyquinolizinium bromide in variable yields (43–56%), and similar results were obtained on replacing ethanol by methanol as the solvent (Table 1, entry 6). Only under aqueous conditions did the reaction proceed, although in this case further difficulties arose because the coupling product was highly soluble in the reaction medium, and it was difficult to purify. Consequently, the yield of the isolated compound was only moderate (56% in the best case).

Attempts to find more suitable conditions for the isolation and purification of the cross-coupling product led us to exchange the counterion in a search for a less soluble salt that could be isolated more easily from the aqueous medium. Fortunately, one of the various counterions tested, hexafluorophosphate gave a salt that was quite insoluble in water, thus allowing the isolation of **2a** in good yield with a high degree of purity by simple filtration (Table 1, entry 8). In a typical experimental procedure, the bromide salt of **2a**

formed in the reaction medium was treated with ammonium hexafluorophosphate to give the hexafluorophosphate salt as a brown precipitate in 76% yield.

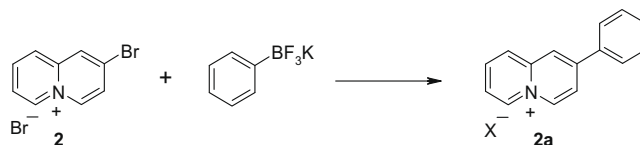
This promising result led us to examine the generality of the process for the other three bromoquinolizinium isomers **1**, **3**, and **4**. The results are summarized in Table 2. The reaction conditions proved to be more efficient for the preparation of the four isomeric phenylquinolizinium compounds than those used previously under the Suzuki and Stille conditions,^{7c} with yields clearly improved in all cases (yields for the Stille couplings are shown in brackets in Table 2). The lower yield obtained for **4a** is a result, at least in part, of the low purity of this compound when isolated directly by filtration from the reaction medium. Further purification by column chromatography was needed to separate this compound from other salts and as a consequence, the isolated yield of the pure compound was somewhat lower than those obtained for **1a**, **2a**, and **3a**.

As stated above, all our previous attempts to carry out the coupling reaction of bromoquinolizinium salts with sp^3 -hybridized carbons on the stannane failed as they were unsuitable coupling partners. However, under the optimized conditions for **2a**, we found that the reaction of potassium benzyltrifluoroborate with **1–4** afforded the corresponding four coupled products **1b–4b** in moderate yield.

Encouraged by these successful results, we sought to apply the method to the preparation of vinyl quinolizinium salts, which are interesting substrates as potential partners in Heck reactions to prepare quinolizinium-based NLO-catiophores. These quinolizinium derivatives were obtained in very low yields in the Stille coupling conditions on positions C-2 and C-3 of the quinolizinium system, and the reaction failed in the C-4 position. Now the coupling reaction between potassium vinyltrifluoroborate¹¹ and **1–4** afforded moderate or good yields of the four isomeric vinylquinoliziniums **1c–4c**.

Finally, studies concerning the scope of the aryl component in the reaction were undertaken. In addition to phenyltrifluoroborate, aryltrifluoroborates bearing electron-donating and electron-withdrawing groups and a heteroaryltrifluoroborate were also examined. Not surprisingly, bromoquinoliziniums **1–4** coupled cleanly using our standard conditions with high yields being obtained if the coupling product can be isolated by simple filtration and lower yields being achieved if further purification was needed (Table 2, see **1e** vs **2–4e**).

Table 1
Optimization of the Synthesis of **2a**



Entry	Catalyst	Reaction conditions	Yield ^a (%)
1	4% $\text{Pd}_2(\text{dba})_3/8\%$ $\text{P}(o\text{-tol})_3$	1.5 equiv K_2CO_3 , DMF, rt, Ar., 24 h	NR
2	4% $\text{Pd}_2(\text{dba})_3/8\%$ $\text{P}(o\text{-tol})_3$	1.5 equiv K_2CO_3 , DMF, 80 °C, Ar, 24 h	Traces
3	4% $\text{Pd}_2(\text{dba})_3/8\%$ biphenyl <i>tert</i> butylphosphine	1.5 equiv K_2CO_3 , DMF, rt, Ar., 24 h	Traces
4	0.5% $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	3 equiv Et_3N , EtOH, reflux, 19 h	Dec ^b
5	0.5% $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	3 equiv (iPr) ₂ EtN, MeOH, reflux, 19 h	Dec ^b
6	1% $\text{Pd}(\text{OAc})_2$	3 equiv K_2CO_3 , EtOH/ H_2O , 65 °C, 5 h	— ^c
7	1% $\text{Pd}(\text{OAc})_2$	3 equiv K_2CO_3 , H_2O , 65 °C, 5 h	56
8	1% $\text{Pd}(\text{OAc})_2$	3 equiv K_2CO_3 , H_2O , 65 °C, 5 h, then H_4NPF_6	76

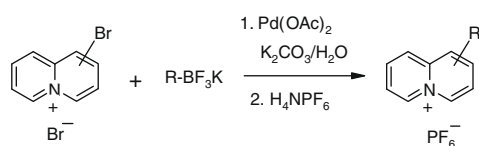
NR: no reaction.

^a Yields of isolated product.

^b Decomposition.

^c From this reaction 4-ethoxy quinolizinium was formed (43–56% yield).

Table 2
Cross-coupling reactions of potassium organotrifluoroborates with bromo quinolizinium bromides **1–4**



	1	2	3	4
	 1a 93% (34%)	 2a 76% (60%)	 3a 74% (53%)	 4a 24% (10%) ^a
	 1b 48% ^a	 2b 64% ^a	 3b 39% ^a	 4b 67%
	 1c 72% (55%)	 2c 71% (10%)	 3c 70% (22%)	 4c 53% (0%)
	 1d 93%	 2d 71% ^a	 3d 77%	 4d 63% ^a
	 1e 91%	 2e 43% ^a	 3e 54% ^a	 4e 40% ^a
	 1f 76%	 2f 98%	 3f 83%	 4f 56%

For all compounds, yields are given for isolated products as the hexafluorophosphate. Yields in brackets are referred to those obtained under Stille cross-coupling conditions.
^a Compounds were further purified by column chromatography.

In conclusion, we have demonstrated that organotrifluoroborates can be used as efficient partners for the Suzuki coupling reaction with the four isomeric bromo quinolizinium bromides. This cross-coupling reaction allows the synthesis of new quinolizinium derivatives, which were not achieved by the Stille reaction or clearly improves the yields of those previously obtained by this reaction. Moreover, the ease with which these potassium organotrifluoroborates reacted with quinolizinium salts in water and the coupling products can be isolated is a further advantage of the procedure and provides a new means for accessing a great variety of substituted azonia cations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.01.040](https://doi.org/10.1016/j.tetlet.2009.01.040).

References and notes

- (a) Rentzepis, P. M.; Pao, Y.-H. *Appl. Phys. Lett.* **1964**, *5*, 156–158; (b) Heilmeyer, G. H.; Ockman, N.; Braunstein, R. J.; Kramer, D. A. *Appl. Phys. Lett.* **1964**, *5*, 229–230.
- (a) *Nonlinear Optics of Organic Molecules and Polymers*; Nalwa, H. S., Miyate, D., Eds.; CRC Press: Boca Raton, 1997; (b) Gonzalez, M.; Segura, J. L.; Seoane, C.; Martin, N.; Garín, J.; Orduña, J.; Alcalá, R.; Villacampa, B.; Hernández, V.; Lopez Navarrete, J. T. *J. Org. Chem.* **2001**, *66*, 8872–8882.
- (a) Marder, S. R.; Perry, J. W.; Yakymyshyn, C. P. *Chem. Mater.* **1994**, *6*, 1137–1147; (b) Coradin, T.; Nakatani, K.; Ledoux, I.; Zyss, J.; Clément, R. *J. Mater. Chem.* **1997**, *7*, 853–854; (c) Coe, B. J.; Harris, J. A.; Brunschwig, B. S.; Garín, J.; Orduña, J. *J. Am. Chem. Soc.* **2005**, *127*, 3284–3285.
- (a) Marder, S. R.; Perry, J. W.; Schaefer, W. P. *Science* **1989**, *245*, 626–628; (b) Lee, O.-K.; Kim, K.-S. *Photon. Sci. News* **1999**, *4*, 9–20; (c) Kaino, T.; Cai, B.; Takayama, K. *Adv. Funct. Mater.* **2002**, *12*, 599–603; (d) Taniuchi, T.; Nakanishi, H.; Ito, H. *Optronics* **2004**, *275*, 135–140.
- (a) Ihmels, H.; Faulhaber, K.; Vedaldi, D.; Dall'Acqua, F.; Viola, G. *Photochem. Photobiol.* **2005**, *81*, 1107–1115; (b) Ihmels, H. *Sci. Synth.* **2005**, *15*, 907–945.
- Tatiana Cañeque (Thesis). Unpublished results.
- (a) Barchin, B. M.; Valenciano, J.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **1999**, *1*, 545–548; (b) García-Cuadrado, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Synlett* **2002**, *11*, 1904–1906; (c) García-Cuadrado, D.; Cuadro, A. M.; Barchin, B. M.; Nunez, A.; Cañeque, T.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2006**, *71*, 7989–7995; (d) Garcia-Cuadrado, D.; Cuadro, A. M.; Alvarez-Builla, J.; Sancho, U.; Castaño, O.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 5955–5958.
- (a) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2004**, *6*, 4125–4127; (b) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Chem. Commun.* **2006**, 2690–2692; (c) Nunez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2007**, *9*, 2977–2980.
- For leading references, see: (a) Darses, S.; Genet, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393–4396; (b) Darses, S.; Michaud, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, *8*, 1875–1883; (c) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103; (d) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870; (e) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.
- For reviews, see: (a) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313–4327; (b) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49–56; (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286; (d) Stefani, H. A.; Cella, R.; Adriano, S. *Tetrahedron* **2007**, *63*, 3623–3658; (e) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–305.
- (a) Darses, S.; Michaud, G.; Genet, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045–5048; (b) Molander, G. A.; Rodríguez-Rivero, M. *Org. Lett.* **2002**, *4*, 107–109.