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Sonogashira Reaction on Quinolizium Cations

Domingo García, Ana M. Cuadro,* Julio Alvarez-Builla, and Juan J. Vaquero*

Departamento de Química Orgánica, Universidad de Alcalá,
28871-Alcalá de Henares, Madrid, Spain

juanjose.vaquero@uah.es

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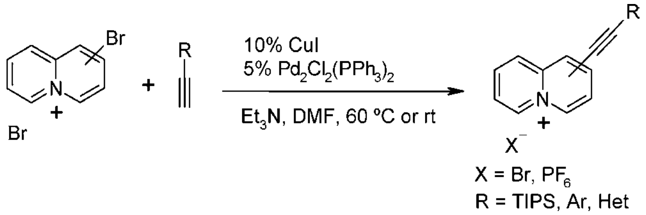
ABSTRACT



The four isomeric bromoquinolizium bromides reacted with aryl- and heteroarylacetylenes under Sonogashira conditions. The reactions proceed with moderate-to-high yields to afford aryl- and heteroarylethynyl quinolizium cations. This is the first reported example of the Sonogashira reaction on heteroaromatic cations, and it allowed easy access to potential π-donor π-acceptor systems bearing cationic units.

Since it was introduced 30 years ago, the Sonogashira palladium-catalyzed cross-coupling reaction[1] has emerged as one of the most straightforward and powerful methods for the preparation of conjugated alkynes.[2] The numerous modifications of the original protocol and the improvement of many aspects of the sp-sp^2 carbon bond formation have led to the wide applicability of this reaction in the synthesis of a variety of compounds,[2a] including different heterocycles,[3] and have made it a useful method for the synthesis of building blocks employed in the preparation of shape-persistent macrocycles,[4] molecular electronic devices,[5] dendrimers,[6] etc.

We became interested in the Sonogashira reaction when we explored the feasibility of incorporating a heteroaromatic cation as a subunit in push−pull systems with nonlinear optical (NLO) properties.[7] The aim of the work was to study the effect of the presence of a charged moiety in these π-donor π-acceptor (D-π-A) molecules[8] (Figure 1). A cross-coupling route involving a heteroaromatic cation as a nucleophilic or electrophilic partner has not been described to date. In this communication we report our initial results for the Sonogashira cross-coupling reaction on quinolizinium cations.[9] This process allowed easy access to a series of the simplest potential D-π-A cationic systems.

Our plan involved the preparation of the four isomeric bromoquinolizium bromides **5a−d** according to literature procedures.[10] Two alternative routes were explored to the target systems **1−4**. The most versatile method involved an initial Sonogashira reaction to incorporate a protected ethynyl

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(1) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *Chem. Commun.* **1977**, 291. (c) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

(2) (a) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, 42, 1566. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (c) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998.

(3) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Tetrahedron Organic Chemistry Series; Pergamon: Amsterdam, 2000; Vol. 20.

(4) (a) Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807. (b) Grave, C.; Schluter, A. D. *Eur. J. Org. Chem.* **2002**, 3075. (c) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81−130. (d) Höger, S. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2685. (e) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402.

(5) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791

(6) (a) Itoh, T.; Maemura, T.; Ohtsuka, Y.; Ikari, Y.; Wildt, H.; Hirai, K.; Tomioka, H. *Eur. J. Org. Chem.* **2004**, *14*, 2949. (b) Heuzé, K.; Méry, D.; Gauss, D.; Astruc, D. *Chem. Commun.* **2003**, 2274. (c) Diez-Barra, E.; Garcia-Martinez, J. C.; Rodriguez-Lopez, J. *J. Org. Chem.* **2003**, *68*, 832. (d) Wang, J.; Lu, M.; Pan, Y.; Peng, Z. *J. Org. Chem.* **2002**, *67*, 7781. (e) Zeng. F.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326

(7) (a) Metzger, R. M. *Chem. Rev.* **2003**, 3803. (b) Carroll R. L.; Gorman C. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 4378. (c) Prasad, P.; Williams, D. *Introduction to Nonlinear Optical Effects In Molecules & Polymers*; John Wiley & Sons: New York, 1991.

10.1021/ol048368e CCC: $27.50

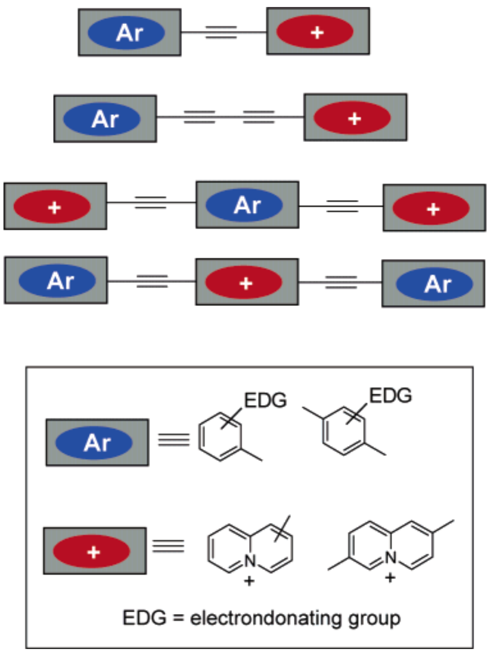
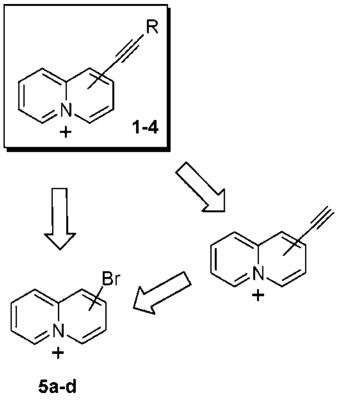


Figure 1. Examples of π-donor π-acceptor (D-π-A) molecules incorporating quinolizium units.

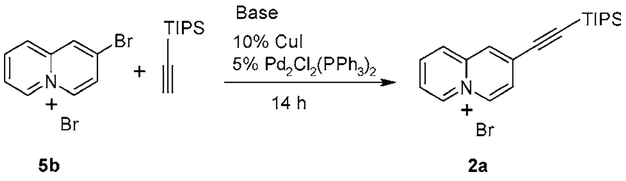
group in all possible positions of the quinolizium system followed by sequential deprotection and a second Sonogashira reaction with an aryl halide to incorporate the aromatic donor system (Scheme 1). In the other route, the corresponding bromoquinolizium salt would be coupled with an aryl-substituted acetylene under Sonogashira conditions.

Scheme 1



2-Bromoquinolizinium bromide (**5b**) was used as a model system to optimize the conditions for the palladium-catalyzed cross-coupling reaction with triisopropylsilylacetylene (TIPSA) using the classical catalytic system CuI/$PdCl_2(PPh_3)_2$, various solvents, bases, equivalents of base, and temperature. The results of this study are shown in Table 1.

Table 1. Sonogashira Reaction of 2-Bromoquinolizinium Bromide (**5b**) and Triisopropylsilylacetylene

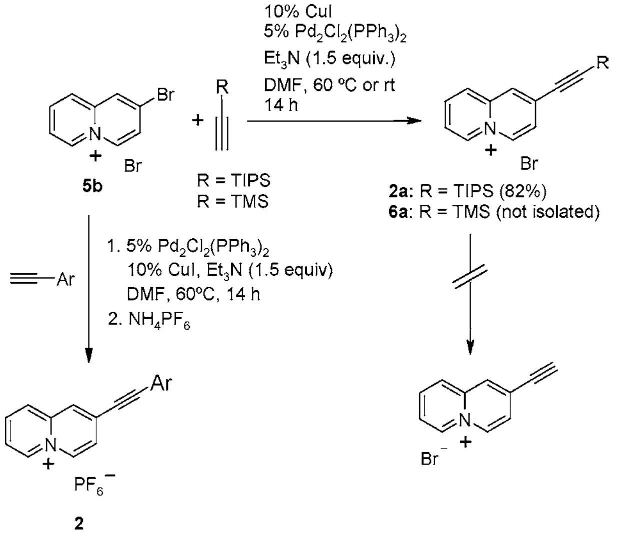


entry	solvent	*T* (°C)	base (equiv)	ratio[a] **5b/2a**
1	DMF	rt	Et_3N (1.2)	1.0:0.8
2	DMAC	rt	Et_3N (1.2)	1.0:0.5
3	DMF	rt	$(i\text{-}Pr)_2NH$ (1.2)	1.0:0.3
4	DMF	rt	$(i\text{-}Pr)_2EtN$ (1.2)	1.0:0.4
5	DMF	rt	Et_3N (20.0)	*b*
6	DMF	60	Et_3N (1.2)	0.3:1.0
7	DMF	60	Et_3N (1.5)	0.08:1.0

[a] Determined by ^1H NMR. [b] Decomposition.

The best conditions were found to be 10 mol % of copper(I) iodide/5 mol % $PdCl_2(PPh_3)_2$ in DMF at 60 °C, with 1.5 equiv of Et_3N for 14 h (Table 1, entry 7). Under these conditions **2a** was isolated in 82% yield. Attempted deprotection of **2a** under the usual conditions (TBAF, CsF) in THF at room temperature or below led to extensive decomposition. The coupling of **5b** with trimethylsilylacetylene afforded **6a** (not isolable), but the attempted in situ deprotection of this alkyne was unsuccessful under a variety of different conditions[11] (Scheme 2).

Scheme 2



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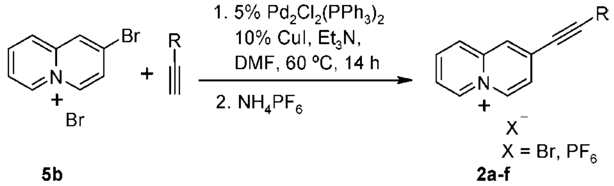
(8) For previous works of charged systems in this field, see: (a) Clays, K.; Coe, B. J. *Chem. Mater*. **2003**, *15*, 642. (b) González, M.; Segura, J. L.; Seoane, C.; Martín, N. *J. Org. Chem.* **2001**, *66*, 8872. (c) Lambert, C.; Gaschler, W.; Nöll, G.; Weber, M.; Schmälzlin, E.; Bräuchle, C.; Meerholz, K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 964. (d) Lambert, C.; Stadler, S.; Bourhill, G.; Bräuchle, C. A*ngew. Chem., Int. Ed. Engl.* **1996**, *35*, 644.

(9) For previous works on palladium-catalyzed reactions on heteroaromatic cations, see: (a) Barchín, B. M.; Valenciano, J.; Cuadro, A. M.; Álvarez-Builla, J.; Vaquero, J. J. *Org. Lett*. **1999**, *1*, 545. (b) Garcia, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Synlett* **2002**, *11*, 1904.

(10) (a) Sanders, G. M.; van Dijk, M.; van der Plas, H. C. *Heterocycles* **1981**, *15*, 213. (b) Glover, E. E.; Jones, G. *J. Chem. Soc*. **1958**, 3021.

Table 2. Sonogashira Reaction on 2-Bromoquinolizinium Bromide (**5b**)



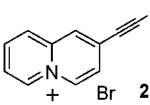
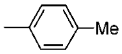
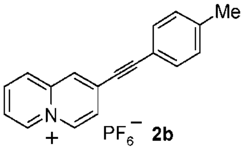
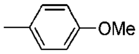
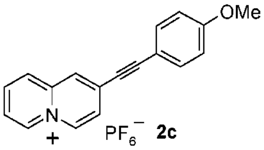
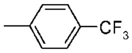
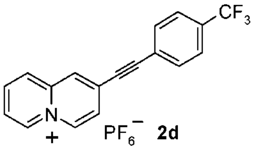
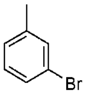
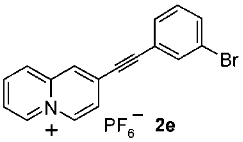
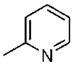
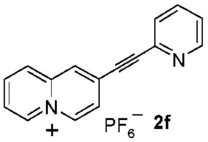
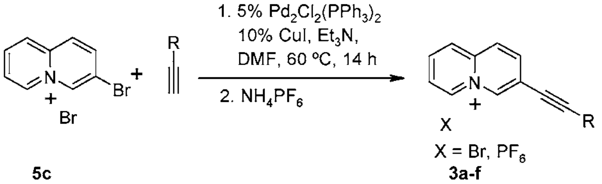
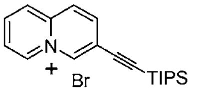
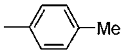
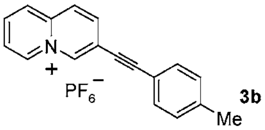
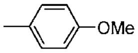
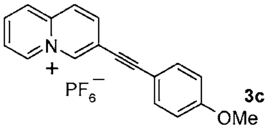
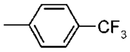
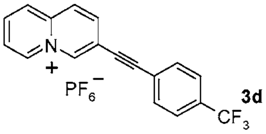
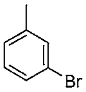
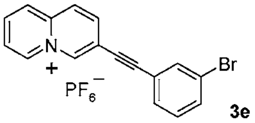
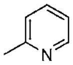
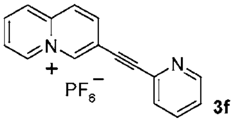
entry	R	coupling product	yield (%)
1	-TIPS	 **2a**	82
2		 **2b**	74
3		 **2c**	78
4		 **2d**	69
5		 **2e**	71
6		 **2f**	43

Table 3. Sonogashira Reaction on 3-Bromoquinolizinium Bromide (**5c**)



entry	R	coupling Product	yield (%)
1	-TIPS	 **3a**	80
2		 **3b**	76
3		 **3c**	77
4		 **3d**	58
5		 **3e**	70
6		 **3f**	50

Consequently, we focused our attention on the coupling reaction of **5b** with arylacetylenes, although this approach to **2** suffers the drawback of the small number of commercially available terminal acetylenes. Under the optimized conditions found for **2a**, 2-bromoquinolizium bromide (**5b**) reacted with different arylacetylenes to give the coupling products in yields of up to 70%. In general, acetylenes bearing electron-donating substituents afforded better yields (Table 2, entries 2 and 3) than those bearing electron-withdrawing groups (Table 2, entries 4 and 5) or when π-deficient heterocycles such as pyridine were attached to the acetylene (Table 2, entry 6). It is worth noting that the high reactivity of **5b** precluded the formation of polymerization products, which are prone to appear under Sonogashira conditions using substrates such as 1-bromo-3-ethynylbenzene.

Having demonstrated that **5b** can act as an efficient partner in the Sonogashira reaction, we investigated the scope of the reaction with the other three bromoquinolizium cations. Significant differences were not found in the reaction of 3-bromoquinolizinium bromide (**5c**) with the same acetylenes as used in the study with **5b**. As shown in Table 3, the best yield was also obtained with triisopropylsilylacetylene and yields obtained with aryl or heteroaryl acetylenes show the same trend as found in the coupling reaction with **5b**. Thus, better yields are associated with the use of electron-rich acetylenes, and 2-pyridylacetylene is the poorest cross-coupling partner, although in this case the yield obtained is slightly higher than that obtained with **5b**.

Finally, we examined the Sonogashira couplings of 1-bromoquinolizium bromide (**5a**) and 4-bromoquinolizinium bromide (**5d**) with two representative examples of acetylene bearing electron-donating and electron-withdrawing substituents. The C4 position is highly activated for the coupling

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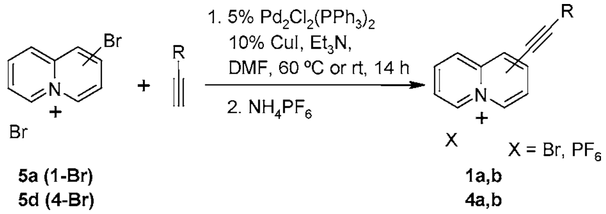
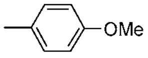
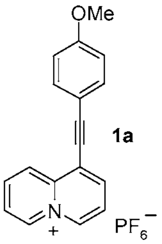
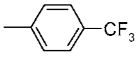
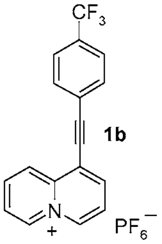
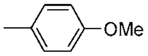
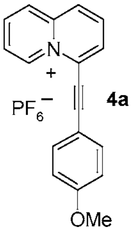
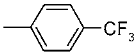
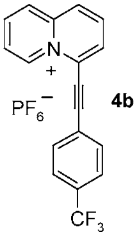
(11) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199.

Table 4. Sonogashira Coupling Reaction on 1-Bromoquinolizium Bromide (**5a**) and 4-Bromoquinolizinium Bromide (**5d**)



entry	R	coupling Product	yield (%)
1		 **1a**	47
2		 **1b**	40
3		 **4a**	61
4		 **4b**	50

reaction but is also activated toward nucleophilic attack. This is the most likely reason that the reaction with 1-ethynyl-4-methoxybenzene proved troublesome under the same conditions as used for the isomeric 2- and 3-bromoquinolizium salts. On heating the reaction at 60 °C we observed extensive decomposition of **5d** and the coupling compound **4a** was obtained in only 25% yield. When the reaction was conducted at room temperature, compound **4a** was isolated in 61% yield (Table 4, entry 3). Lower temperatures did not improve this yield, and longer reaction times were necessary to complete the reaction. In all of the reactions involving the other arylacetylenes tested, the corresponding halide was completely consumed but only moderate yields (40−50%) of the coupling product were obtained. These lower yields, when compared with those obtained with **5b**,**c**, are probably due to the lower stability of these substrates under the reaction; indeed, mixtures of the ring-opening products are observed in all of these reactions.

In conclusion, we have demonstrated that the four isomeric bromoquinolizium cations can be used as electrophilic partners in Sonogashira reactions. The protocol developed allows the efficient incorporation of aryl- and heteroarylethynyl substituents into the quinolizium system, particularly at the C2 and C3 positions.[12] Furthermore, the methodology described here opens an easy way to access potential π-donor π-acceptor (D-π-A) systems that incorporate one or more heteroaromatic cationic units. Investigation of the properties of these molecules is now in progress.

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Supporting Information Available: Experimental procedures and characterization data for isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **Typical Experimental Procedure**. A flame-dried vial was charged under argon with 50 mg (0.173 mmol) of the corresponding bromoquinolizinium salt **5a**−**d**, 10 mol % CuI (3.3 mg, 0.0173 mmol), and 5 mol % $PdCl_2(PPh_3)_2$ (6.9 mg, 0.0087 mmol) in dry DMF (2.5 mL). Then the corresponding acetylene (0.208 mmol) and Et_3N (0.259 mmol, 45 μL) were added. After being heated at 60 °C for 14 h, the solution was filtered through a small pad of Celite and washed with methanol (5 mL). The solution was concentrated, treated with a saturated solution of $NaHCO_3$ (20 mL), and extracted with EtOAc (15 mL). The organic phase was extracted with H_2O (2 × 10 mL), the aqueous phase was treated with a saturated solution of NH_4PF_6, and the resulting phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the product was isolated by column chromatography on silica gel using CH_2Cl_2/MeOH (9.6:0.4) as eluent.