

First Synthesis of Biquinolizinium Salts: Novel Example of a Chiral Azonia Dication

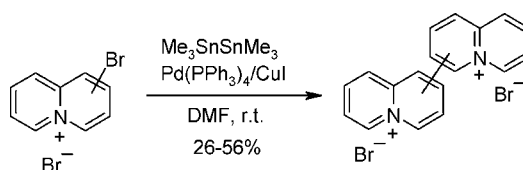
Domingo García-Cuadrado,[†] Ana M. Cuadro,^{*†} Julio Alvarez-Builla,[†]
Unai Sancho,[‡] Obis Castaño,[‡] and Juan J. Vaquero^{*†}

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

juanjose.vaquero@uah.es

Received September 20, 2006

ABSTRACT



The 1,1'-, 2,2'-, and 3,3'-biquinolizinium dications are described for the first time and were prepared using palladium-catalyzed homocoupling reactions of the corresponding isomeric bromoquinolizinium bromides. Theoretical calculations show 1,1'- and 4,4'-biquinolizinium dications to be chiral molecules, the latter of which has a high energy of formation, a factor that probably precludes its formation.

Biaryls and biheteroaryls are significant building blocks in a large number of natural products¹ and pharmacophores in a variety of biologically active compounds.² Some advanced materials such as conductive polymers³ and liquid crystals,⁴ supramolecules,⁵ and asymmetric catalysts⁶ are also based on biaryl units. Viologens represent an important class of charged biheteroaryls based on the 4,4'-bipyridinium unit.

These materials have found applications in electrochromism, solar energy conversion, and molecular electronics.⁷

Quinolizinium,⁸ the simplest cation containing a bridgehead quaternary nitrogen, has been known since 1954,⁹ but biquinoliziniums remained unknown despite the fact that these bicationic species could have applications similar to those found for their bipyridinium analogues (Figure 1). In this communication we describe the first synthesis of 1,1'-, 2,2'-, and 3,3'-biquinolizinium cations¹⁰ along with a theoretical study on their structure and the rotational barriers around the σ

[†] Departamento de Química Orgánica.

[‡] Departamento de Química Física.

(1) Bringmann, G.; Ochse, M.; Schupp, O.; Tasler, S. In *Progress in the Chemistry of Organic Natural Products*; Springer: Wien, 2001; Vol. 82.

(2) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Wang, G. T.; Wang, S.; Gentles, R.; Sowin, T.; Leitza, S.; Reilly, E. B.; von Geldern, T. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 195.

(3) (a) Yamamoto, T.; Maruyama, T.; Zhou, Z.; Ito, T.; Fukada, T.; Yoneda, Y.; Begum, F.; Ikeda, T.; Sasaki, S.; Takezoe, H.; Fukada, A.; Kubota, K. *J. Am. Chem. Soc.* **1994**, *116*, 4832. (b) Schulz, E.; Fahmi, K.; Lemaire, M. *Acros Org. Acta* **1995**, *1*, 10. (c) Zhu, S. S.; Swager, T. M. *Adv. Mater.* **1996**, *8*, 497. (d) Papillon, J.; Schulz, E.; Gelinat, S.; Lessard, J.; Lemaire, M. *Synth. Met.* **1998**, *96*, 155.

(4) Manka, J. T.; Guo, F.; Huang, J.; Yin, H.; Farrar, J. M.; Sienkowska, M.; Benin, V.; Kaszynski, P. *J. Org. Chem.* **2003**, *68*, 9574.

(5) *Supramol. Chem.*, 1st ed.; Lehn, J. M., Ed.; VCH: Weinheim, Germany, 1995.

(6) For the use of BINAP ligands, see the Nobel lecture: Asymmetric catalysis: Science and opportunities. Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(7) (a) *The Viologens*; Monk, P. S. M., Ed.; John Wiley: Canada, 1999. (b) Stoddart, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 164. (c) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (d) Stoddart, J. F. *Acc. Chem. Res.* **2001**, *34*, 410. (e) Benniston, A. C.; Harriman, A.; Li, P.; Rostron, J. P. *Tetrahedron Lett.* **2005**, *46*, 7291. (f) Branowska, D.; Rykowski, A.; Wysocki, *Tetrahedron Lett.* **2005**, *46*, 6223. (g) Coe, B. J.; Harris, B. J.; Brunschwig, J. A.; Garin, B. S. W.; J.; Orduña, J. *J. Am. Chem. Soc.* **2005**, *127*, 3284. (h) Dichtel, W. R.; Miljanic, O. S.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388. (i) Badjic, J. D.; Ronconi, C. M.; Stoddart, J. F.; Balzani, V.; Silvi, S.; Credi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1489.

(8) For the most recent review, see: Ihmels, H. *Quinolizinium Salts and Benzo Analogues in Science of Synthesis*; Black, D., Ed.; Georg Thieme Verlag: Stuttgart, 2004; Vol. 15, pp 907–946.

(9) Boekelheide, V.; Gall, W. G. *J. Am. Chem. Soc.* **1954**, *76*, 1832.

(10) For the only precedent of a bibenzoquinolizinium, see: Bradsher, C. K.; Yarrington, N. L. *J. Org. Chem.* **1963**, *28*, 78.

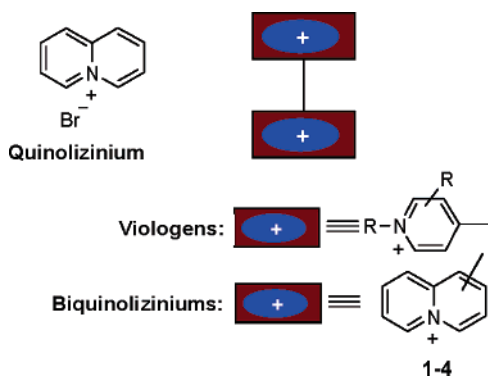
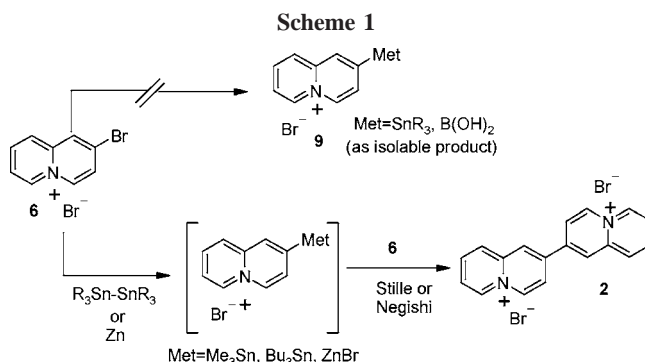


Figure 1. Quinolizinium and heteroaromatic bication.

bond. Results show the 1,1'- and 4,4'-biquinolizinium dibromides to be chiral dication; the very high formation energy of the latter probably accounts for the failure of its preparation.

Typical methods for the preparation of biaryl compounds include the reductive homocoupling of aryl-halides in the classical Ullmann reaction.¹¹ More recently, palladium-catalyzed coupling reactions of aryl halides with organometallic compounds¹² based on tin, boron, and zinc have emerged as the methods of choice. Recently, several studies on the synthesis of symmetrical biaryls have been reported, and these reflect the current efforts in this field of research.¹³

Based on the palladium-mediated strategy, our initial approach to achieve the biquinolizinium cations **1–4** was to convert the four known isomeric bromoquinolizinium cations **5–8**¹⁴ into the heteroaryl tin, heteroarylboronic acid, and heteroaryl zinc derivatives¹² in order to test the well-known Stille, Suzuki, and Negishi reactions with these haloquinolizinium salts. All of our attempts to isolate the tributylquinolizinium tin and the quinolizinium boronic acid (**9**) from the 2-bromo-quinolizinium bromide **6** used as a model failed (Scheme 1). However, we observed that the homocoupling reaction did occur in attempts to generate the quinolizinium zinc bromide and the tributylquinolizinium tin. Comparison of the results of these two homocoupling processes showed that yields of the homocoupled compound were higher on using the stannylation reaction in comparison



to those obtained by formation of the quinolizinium zinc bromide. These results led us to focus our efforts on optimizing the reaction conditions of the palladium-catalyzed stannylation of **6**; the results are shown in Table 1.

Table 1. Optimization of the Synthesis of **2** under Stille Conditions

| entry | catalytic system ^a | (R ₃ Sn) ₂ | equiv | 2 (yield %) |
|-------|-------------------------------|-----------------------------------|-------|--------------------|
| 1 | A | (Me ₃ Sn) ₂ | 0.5 | 39 |
| 2 | A | (Me ₃ Sn) ₂ | 1.3 | 49 |
| 3 | A | (Me ₃ Sn) ₂ | 2 | 50 |
| 4 | A | (Me ₃ Sn) ₂ | 1.3 | 52 ^b |
| 5 | A | (Me ₃ Sn) ₂ | 1 | 56 ^b |
| 6 | B | (Bu ₃ Sn) ₂ | 1 | 50 |

^a A: 10 mol % CuI, 5 mol % Pd(PPh₃)₄. B: 5 mol % Pd₂(dba)₃, 5 mol % P(*o*-Tol)₃. ^b Slow addition of **6**.

The results show that the homocoupling product is formed using different stoichiometric quantities of hexamethyldistannane (entries 1–4), and 0.5 equiv of this reagent did not afford the best yield as one would have expected. The use of 1 equiv of hexamethyldistannane, 10 mol % CuI, and 5 mol % Pd(PPh₃)₄ as the catalytic system afforded a better yield of **2**, and this was slightly improved by the slow addition of **6** (entry 5). Other catalytic systems, such as 5 mol % Pd₂(dba)₃ and 5 mol % P(*o*-Tol)₃ with 1 equiv of hexabutylstannane, did not improve the yield of the homocoupled product.

The coupling reactions using these conditions were also successful for 1,1'- and 3,3'-biquinolizinium compounds **1** and **3**, although **1** was obtained in lower yield.¹⁵ However, despite the fact that different conditions were tested, the 4,4'-biquinolizinium **4** was not formed and all attempts gave the

(15) **Synthesis of 1–3. General Procedure.** To a solution of the corresponding bromoquinolizinium bromides **5–7** (100 mg, 0.346 mmol) and 10 mol % CuI (6.6 mg, 0.0346 mmol) in dry DMF (3 mL) under argon were added hexamethyldistannane (113.3 mg, 0.346 mmol) in dry DMF (2 mL) and Pd(PPh₃)₄ (20.0 mg, 0.0173 mmol), and the reaction mixture was stirred at room temperature for 22 h. Next, the solution was concentrated under reduced pressure, and the residue was treated with 3 mL of EtOH (**1** and **3**) or THF (**2**). The solid was filtered and washed with ethanol (**1** and **3**) or EtOAc (**2**). Purification of the crude product by column chromatography on silica gel (reverse phase) using water as eluent yielded the corresponding biquinolizinium dibromides **1–3**.

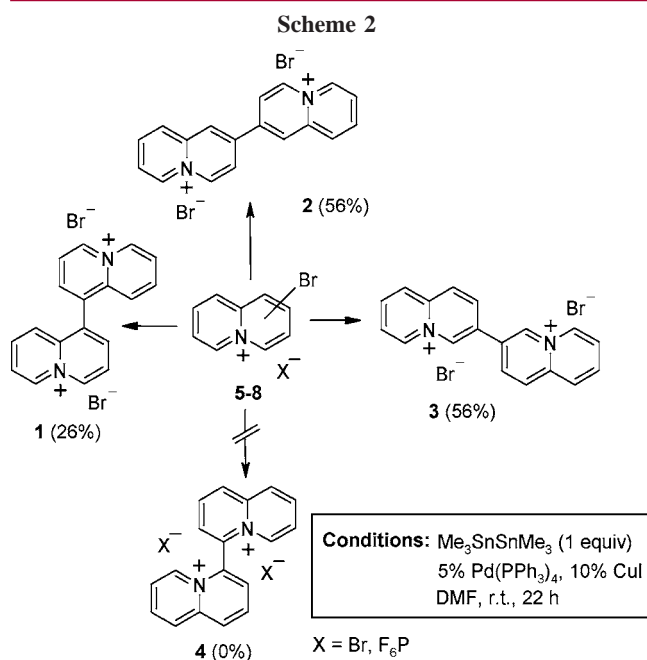
(11) (a) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174. (b) Li, J. H.; Xie, Y. X.; Yin, D. L. *J. Org. Chem.* **2003**, *68*, 9867 and references therein.

(12) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (d) Percec, V.; Bae, J.-Y.; M., Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176. (e) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(13) (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Nising, C. F.; Schmid, U. K.; Nieger, M.; Bräse, S. *J. Org. Chem.* **2004**, *69*, 6830. (c) Demir, A. S.; Reis, O.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 10130. (d) Abiraj, K.; Srinivasa, G. R.; Channe Gowda, D. *Tetrahedron Lett.* **2004**, *45*, 2081. (e) Li, J.-H.; Xie, Y.-K.; Yin, D.-L. *J. Org. Chem.* **2003**, *68*, 9867. (f) Bringmann, G.; Price, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.

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

dehalogenated starting material (quinolizinium) as the main product, even when the counterion was changed to hexafluorophosphate (Scheme 2).



The formation of 2,2'- and 3,3'-quinolizinium systems from 2-bromo- and 3-bromoquinolizinium, which present different electronic characters, does not have a large effect on the yields (56% for each bication). By contrast, the lower yield of **1** from the homocoupling of 1-bromoquinolizinium, in which the bromo atom is in a position electronically similar to C3, can be attributed to its sterically hindered structure (see below). Steric hindrance, along with a stronger charge repulsion, could explain the unsuccessful coupling of 4-bromoquinolizinium to form 4,4'-biquinolizinium (**4**).

An ab initio theoretical study¹⁶ of the four isomeric biquinoliziniums (**1–4**) shows that in compounds **1** and **4** the *syn* rotation around the ring–ring bond is forbidden by a high energy barrier. This is due to the large distortion in the molecules in order that the quinolizinium moieties may pass by each other. In these cases only two minima, a pair of enantiomers, were found and these had twist angles of $\pm 94^\circ$ (for **1**) and $\pm 86^\circ$ (for **4**). In both processes, the passage of the crucial hydrogens is facilitated by out-of-plane deformation of the two-ring system (Figure 2). Activation

(16) *Gaussian 98*, Revision A.11; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian, Inc.*: Pittsburgh, PA, 2001.

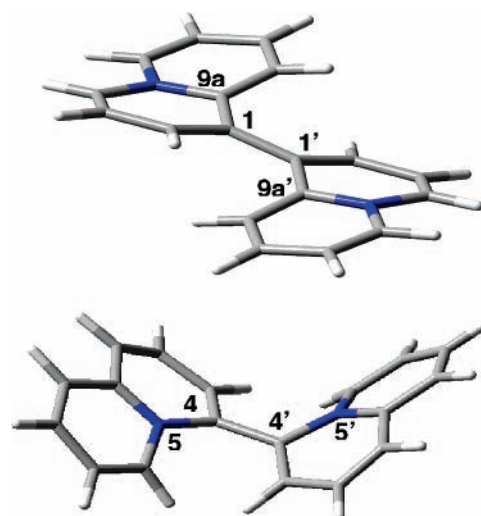


Figure 2. Anti-transition states structures for biquinolizinium **1** (top) and **4** (bottom) showing their out-of-plane deformations.

energy values of 30.7 kcal/mol for **1** and 44.3 kcal/mol for **4** are high enough to preclude racemization. The energy value for **1** is similar to that found for the rotation barrier of binaphthyl (30.0 kcal/mol) at the same level of theory.

In the cases of compounds **2** and **3**, two pairs of enantiomers were identified as minima during the rotation process of these molecules, as summarized in Table 2. The

Table 2. Relative Energies and Geometrical Parameters of Stationary Points of **1–4**

| | dihedral | dihedral angle | $\Delta\Delta E$ HF/6-31G* (kcal/mol) |
|-----------------------------|-------------|-----------------|--|
| 1,1'-Biquinolizinium | | | |
| GS | 9a–1–1'–9a' | 93.87, –93.87 | 0 |
| anti-TS | 9a–1–1'–9a' | 180.00 | 30.73 |
| 2,2'-Biquinolizinium | | | |
| GS1 | 1–2–2'–1' | 49.33, –49.33 | 0 |
| GS2 | 1–2–2'–1' | 135.50, –135.50 | 0.11 |
| <i>syn</i> -TS | 1–2–2'–1' | –0.01 | 3.38 |
| <i>anti</i> -TS | 1–2–2'–1' | 179.99 | 2.61 |
| GS1GS2-TS | 1–2–2'–1' | 93.70, –93.70 | 1.05 |
| 3,3'-Biquinolizinium | | | |
| GS1 | 4–3–3'–4' | 61.28, –61.28 | 0 |
| GS2 | 4–3–3'–4' | 126.24, –126.24 | 0.25 |
| <i>syn</i> -TS | 4–3–3'–4' | 0.00 | 5.43 |
| <i>anti</i> -TS | 4–3–3'–4' | –180.00 | 3.79 |
| GS1GS2-TS | 4–3–3'–4' | 98.65, –98.65 | 0.43 |
| 4,4'-Biquinolizinium | | | |
| GS | 5–4–4'–5' | 86.04, –86.04 | 0 |
| <i>anti</i> -TS | 5–4–4'–5' | –138.38 | 44.30 |

differences in energy between the minima is very low in both compounds (0.1 kcal/mol in **2** and 0.2 kcal/mol in **3**) and so are their energy barriers (1.0 kcal/mol for **2** and 0.4

kcal/mol for **3**). The crucial step in the process must be at twist angles of 0° and 180° because of the high level of steric repulsion. Nevertheless, this step is not as traumatic as those in isomers **1** and **4** (absence of out-of-plane deformation of the ring systems). In fact, the steric repulsion in **2** and **3** is small, as demonstrated by the higher activation energy values (3.4 and 5.4 kcal/mol) corresponding to the *syn* rotation. Racemization at room temperature is expected for both compounds.

The results from this study can be rationalized in terms of steric repulsion and resonance (delocalization). Compounds **2** and **3** are less geometrically restricted than **1** and **4**. This fact allows these molecules to have a higher number of energy minima in the rotational process and also makes steric repulsion a nondeterminant factor. When the molecule is planar, a maximum level of steric repulsion is reached, whereas if quinolizinium rings adopt an orthogonal arrangement, both the steric repulsion and resonance effect would be minimized. If the steric effect is determinant, as it is in **1** and **4**, the minimum energy geometry is reached when both rings are nearly orthogonal. However, if this effect is nondeterminant, the minimum energy geometry would be the result of a compromise between resonance and steric repulsion.

Enthalpies of formation for **1–4** were obtained by MP2/6-31G(d) optimizations on the most stable minima identified. These values are summarized in Table 3 and show that **4** is the least stable compound and, therefore, should be the hardest to form. The low yield obtained for **1** can also be explained in terms of its enthalpy of formation (7.4 and 4.0 kcal/mol higher than the values for **2** and **3**, respectively).

In summary, we describe the first synthesis of symmetrical biquinolizinium cations, which were prepared by a palladium-catalyzed coupling reaction on the corresponding

Table 3. Relative Enthalpies of Formation of **1–4**

| compound | $\Delta\Delta H_{f,298K}$ kcal/mol |
|----------|------------------------------------|
| 1 | 7.42 |
| 2 | 0 |
| 3 | 3.42 |
| 4 | 14.08 |

bromo quinolizinium bromides. Theoretical calculations predict 1,1'- and 4,4'-biquinolizinium dications to be chiral molecules, with the latter having such a high energy of formation that this factor is likely to account for the failure to form this compound. As racemic bication **1** shows good solubility in water, its resolution will open a way to new water-soluble chiral catalysts based on the 1,1'-biquinolizinium cation.

Acknowledgment. The authors acknowledge support of this work from the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Dirección General de Investigación, Ministerio de Ciencia y Tecnología through projects CTQ2005-01060, BQU2003-07281. D.G. is grateful to the Ministerio de Educación y Ciencia for a fellowship. U.S. is grateful to the Comunidad de Madrid and the ESF for a fellowship. We also acknowledge to Dr. M. Galajov for NMR experiments.

Supporting Information Available: ¹H and ¹³C NMR spectra, experimental details, characterization and computational data for **1–4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL062314I