



A novel alkylation procedure using MW irradiation for the synthesis of 1,2,3-trisubstituted 1,4,5,6,7,8-hexahydro-1,3-diazocinium salts from their corresponding 1,2-diaryldiazocines

María A. Ramírez, Gisela M. Ortiz, Alejandra Salerno, Isabel A. Perillo, María M. Blanco*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956 (1113) Buenos Aires, Argentina

ARTICLE INFO

Article history:

Received 5 December 2011

Revised 3 January 2012

Accepted 4 January 2012

Available online 15 January 2012

Keywords:

Cyclic amidinium salts

Cyclic amidines

Ethyl polyphosphate

N-alkylation

Microwaves

ABSTRACT

In this work, we describe the synthesis of a series of 1,2,3-trisubstituted-1,4,5,6,7,8-hexahydro-1,3-diazocinium salts (**1**) by alkylation of the corresponding 1,2-diaryl-1,4,5,6,7,8-hexahydro-1,3-diazocines (**2**). Compounds **2** were obtained by ethyl polyphosphate-promoted cyclocondensation of *N*-aroyl-*N'*-arylpentamethylenediamines (**3**). Reaction of compounds **2** with alkyl iodides led to 1,2,3-trisubstituted 1,4,5,6,7,8-hexahydro-1,3-diazocinium iodides (**1**), a new family of cyclic amidinium salts. The best yields for the alkylation were achieved using a mixture of DCM–DMSO (10:1) as solvent. The reaction times of both, the cyclocondensation of compounds **3** and the reaction of **2** with alkyl halides, are dramatically decreased when using microwave irradiation.

© 2012 Elsevier Ltd. All rights reserved.

N-Substituted derivatives of pentamethylenediamine (cadaverine) are considered the analogs of natural polyamines.¹ Some of them are compounds of interest due to their biological properties. *N*-(*p*-Tolyl) cadaverine is an active fibrin-stabilizing factor (FSF) inhibitor² and *N,N'*-dibenzyl and *N,N'*-di(2-chloroethyl) derivatives show antitumor activity.^{3,4}

One of the strategies used for the synthesis of selectively N-substituted 1,*n*-diamines starts from acyclic compounds that provide the polymethylene portion, generally the corresponding 1,*n*-diamine or some derivative. Thus, for example, *N*-alkyl or benzylpentamethylenediamines are obtained by transforming the amino primary group by means of reductive alkylation using a carbonyl compound.^{1,5} On the other hand, the reaction of cadaverine with reactive chloronitrobenzenes easily leads to the corresponding *N*-nitroaryl derivatives.⁶ In contrast, the synthesis of cadaverines with other types of N-substitution requires more complex synthetic strategies. Among these, we have recently described two new routes for the synthesis of *N*-arylpentamethylenediamines.⁷

An alternative strategy to obtain selectively N-substituted 1, *n*-diamines is to use dinitrogenated heterocyclic compounds such as cyclic amidines^{8–10} (**I**), cyclic amidinium salts¹¹ (**II**), and animal¹² (**III**) as precursors (Fig. 1).

Imidazolines⁸ and their six-⁹ and seven-membered homologs¹⁰ (**I**, *n* = 2–4) and the corresponding imidazolium and tetrahydropyrimidinium salts¹¹ (**II**, *n* = 2,3) have been synthesized and used as synthetic precursors to obtain N-substituted diamines by reductive cleavage of the heterocyclic ring. However, hexahydrodiazocines (**I**, *n* = 5) have not been explored for this purpose. Some of them have been obtained from the reaction of 1,5-diaminopentane and an appropriate compound that provides the C-2 of the cycle¹³ or by cyclocondensation of adequate acyclic precursors.^{6,14} In contrast, to our knowledge, there are no reports of the corresponding hexahydro-1,3-diazocinium salts (**II**, *n* = 5).

In line with our previous studies related to the synthesis of diamine derivatives of biological interest, here we describe the synthesis of a series of eight-membered cyclic amidinium salts, namely 1,2-diaryl-3-methyl-1,4,5,6,7,8-hexahydro-1,3-diazocinium salts (**1**) and their 1,2-diaryl-1,4,5,6,7,8-hexahydro-1,3-diazocines (**2**) precursors (Table 1) as potential sources of selectively *N,N,N'*-tri- and *N,N'*-di-substituted pentamethylenediamines, respectively.

To this end, we used *N*-aroyl-*N'*-arylpentamethylenediamines **3** as precursors of hexahydrodiazocines **2** (Scheme 1). In our first approach, we prepared compounds **3** by acylation of *N*-arylpentamethylenediamines⁷ (Scheme 1). However, the reaction of *N*-phenylpentamethylenediamine with benzoyl chloride under Schotten–Baumann conditions gave poor yields of the desired compound **3**, together with important amounts of unreacted diamine and the corresponding *N,N'*-dibenzoyl derivative. The

* Corresponding author. Tel./fax: +54 11 4964 8250.

E-mail addresses: mercedesblanco2@yahoo.com.ar, mblanco@ffy.uba.ar (M.M. Blanco).

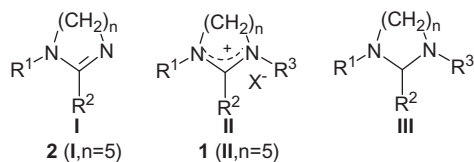


Figure 1. Cyclic amidines (**I**), cyclic amidinium salts (**II**) and amidals (**III**).

Table 1
Compounds **1**, **2** and **3** prepared

Compounds	Ar ¹	Ar ²	R
1a	C ₆ H ₅	C ₆ H ₅	CH ₃
1b	C ₆ H ₅	4-ClC ₆ H ₄	CH ₃
1c	4-CH ₃ C ₆ H ₄	C ₆ H ₅	CH ₃
1d	4-CH ₃ C ₆ H ₄	4-ClC ₆ H ₄	CH ₃
1e	4-ClC ₆ H ₄	C ₆ H ₅	CH ₃
1f	3,4-Cl ₂ C ₆ H ₃	4-ClC ₆ H ₄	CH ₃
1g	C ₆ H ₅	C ₆ H ₅	CH ₂ (4-BrC ₆ H ₄)
1h	3,4-Cl ₂ C ₆ H ₃	4-ClC ₆ H ₄	CH ₂ C ₆ H ₅
2a,3a	C ₆ H ₅	C ₆ H ₅	
2b,3b	C ₆ H ₅	4-ClC ₆ H ₄	
2c,3c	4-CH ₃ C ₆ H ₄	C ₆ H ₅	
2d,3d	4-CH ₃ C ₆ H ₄	4-ClC ₆ H ₄	
2e,3e	4-ClC ₆ H ₄	C ₆ H ₅	
2f,3f	3,4-Cl ₂ C ₆ H ₃	4-ClC ₆ H ₄	

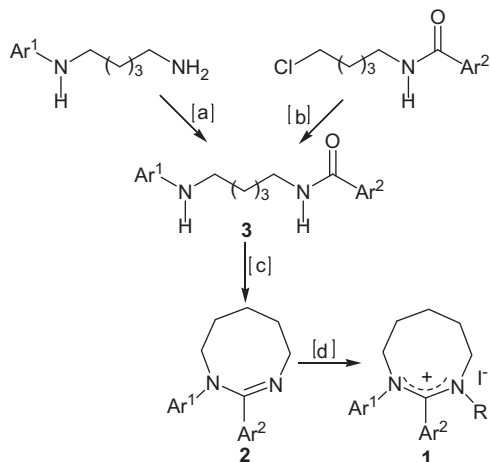
selective acylation of the primary amino group was achieved with 55–60% yields working in homogeneous phase with DCM as solvent and TEA as acceptor of hydrogen chloride at -10°C .

The second approach to obtain compounds **3** involved the use of *N*-(5-chloropentyl) benzamides obtained from piperidine derivatives by von Braun reaction.¹⁵

The reaction, with a two-fold amount of arylamines, led to the expected compounds **3**. The best yields (75–87%) were obtained when heating at 100°C in the absence of solvent.

The ring closure of compounds **3** was assayed using PPE (ethyl polyphosphate) and PPSE (trimethylsilyl polyphosphate) under different conditions. Excellent yields (96–99%) were obtained working with conventional heating with PPE in free-solvent reactions at 120° for 45–60 min. With the aim to optimize the reaction, we used microwave irradiation (MW), a valuable technique which has received increased attention in the last decades.¹⁶ In this work, we used a Microwave Digestion System WX-4000. In chloroform solution at 700 W (70°C), we obtained yields similar to the previous ones in 6–7 min.

As expected because of the nature of cyclic amidines, compounds **2** have nucleophilic character due to the N-3 lone pair. Reactions with alkyl halides led to the corresponding 1,2,3-trisubstituted hexahydro-1,3-diazocinium salts **1**, highly stabilized by resonance (Scheme 1). Since the reaction is a typical S_N2 displacement, it is adequate for the introduction of primary alkyl groups. As alkylating reagents we employed methyl iodide, 4-chlorobenzyl iodide, and benzyl iodide. Since the solvent plays a major role in alkylation reactions, varying both speed and nature of the products,¹⁷ different solvents were tested. Using ethanol, acetonitrile, acetone, THF, and chloroform we obtained in general very poor yields of compounds **1** recovering large amounts of the unreacted amidine. When the reaction was conducted in DCM solution, in some cases, we obtained low yields of salt **1**, the major product being the corresponding hexahydrodiazocine hydrohalide. Improved yields were obtained under strictly anhydrous conditions. Finally, protonation of the amidine could be avoided by using a mixture of DCM–DMSO (10:1) as solvent. Working at reflux with conventional heating, 2–4 h was required for total conversion (71–95%). Using MW irradiation, the reactions were carried out



Scheme 1. (a) Ar²COCl/TEA/DCM/ -10°C . (b) Ar¹NH₂/ 100°C . (c) PPE/ 120°C or PPE/HCCl₃/ 70°C /700 W. (d) RI/DCM–DMSO (10:1)/reflux or RI/HCCl₃/ 90°C /400 W.

in chloroform solution without the addition of the DMSO. In this way the reaction times were reduced to 6–15 min and the workup was easier (85–96%). When we used alkyl chlorides or bromides as alkylation agents, results were not as satisfactory as those presented above. We obtained hygroscopic salts that were hard to purify. Reaction times were longer, both employing conventional heating and MW irradiation, and yields were lower.

Iodides **1** are stable salts. Infrared spectra confirmed their ionic structure, as it can be seen from the strong amidinium band at ca. $1600\text{--}1620\text{ cm}^{-1}$. However, they are oils thus evidencing characteristics of ionic liquids.

Comparing ¹HNMR spectra of compounds **1** and **2** we found certain facts. All methylene hydrogen signals of salts **1** are deshielded with respect to the values of amidines **2**. Methylenes adjacent to the N-1 and N-3 were the most affected ($\Delta\delta = 0.98$ and 0.67 ppm, respectively). The deshielding results from the electron deficiency of the heterocyclic ring caused by nitrogen quaternization are in full agreement with the cationic character of the amidinium system.

In conclusion, we herein report the synthesis of 1,2-diaryl-1,4,5,6,7,8-hexahydro-1,3-diazocines (**2**) and their corresponding 1,2,3-trisubstituted diazocinium salts **1**, a new family of cyclic amidinium compounds. The method used to obtain the diazocines **2** involves the PPE-promoted cyclocondensation of *N*-arylpentamethylenediamines **3**. Two alternative routes for the preparation of compounds **3** are presented. Finally, reaction with alkyl halides leads to salts **1**. We also showed that the reaction times of both, the cyclocondensation of compounds **3** and the reaction of **2** with alkyl halides, are dramatically decreased when using microwave irradiation. Compounds **2** and **1** are potential key intermediates for the synthesis of selectively *N,N'*-di- and *N,N,N'*-trisubstituted pentamethylenediamines.

Acknowledgments

This work was financially supported by the Universidad de Buenos Aires and the Agencia Nacional de Promoción Científica y Tecnológica.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.009.

References and notes

1. Burns, M. R. U.S. Patent 6,872,852, 2005.
2. (a) Stemberg, P.; Ljunggreth, C.; Nilsson, J. L. G.; Lundén, R.; Eriksson, O. *J. Med. Chem.* **1972**, *15*, 674; (b) Ahmad, P.; Fyfe, C. A.; Mellors, A. *Biochem. Pharmacol.* **1975**, *24*, 1103; (c) Hoffmann, K.-J.; Stemberg, P.; Ljunggren, C.; Svensson, U.; Nilsson, J. L. G. *J. Med. Chem.* **1975**, *18*, 278.
3. Aizencang, G.; Harari, P.; Buldain, G.; Guerra, L.; Pickart, M.; Hernández, P.; Frydman, B. *Cell. Mol. Biol.* **1998**, *44*, 615 (and references cited therein); [b] Frydman, B. U. S. Patent 5,677,350, 1997.
4. Lee, W. W.; Berridge, B. J.; Ross, L. O.; Goodman, L. J. *J. Med. Chem.* **1963**, *6*, 567.
5. (a) Burns, M. R.; LaTurner, S.; Ziemer, J.; McVean, M.; Devens, B.; Carlson, C. L.; Graminski, G. F.; Vanderwerf, S. M.; Weeks, R. S.; Carreon, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1263 (and references therein); [b] Chang, Y. H.; Evanega, G. R.; McLamore, W. M. U. S. Patent 3,729,564, 1973.
6. Perillo, I.; Fernández, B.; Lamdan, S. *J. Chem. Soc., Perkin II* **1977**, 2068.
7. (a) Ramírez, M. A.; Corona, M. V.; Blanco, M. M.; Perillo, I. A.; Porcal, W.; Salerno, A. *Tetrahedron Lett.* **2010**, *51*, 5000; (b) Ramírez, M. A.; Corona, M. V.; Ortiz, G.; Salerno, A.; Perillo, I. A.; Blanco, M. M. *Tetrahedron Lett.* **2011**, *52*, 1466 (and references therein).
8. Perillo, I.; Caterina, M. C.; López, J.; Salerno, A. *Synthesis* **2004**, 851.
9. Orelli, L.; Niemezv, F.; García, M. B.; Perillo, I. *J. Heterocycl. Chem.* **1999**, *36*, 105.
10. Hedrera, M.; Perillo, I. A. *J. Heterocycl. Chem.* **2000**, *37*, 1431 (and references therein).
11. (a) Salerno, A.; Ceriani, V.; Perillo, I. *J. Heterocycl. Chem.* **1992**, *29*, 1725; (b) Dal Maso, M.; Orelli, L.; Perillo, I. A. *J. Heterocycl. Chem.* **1994**, *31*, 25; (c) García, M. B.; Zani, M.; Perillo, I.; Orelli, L. *Heterocycles* **2004**, *63*, 2557.
12. (a) Rivera, A.; Rios-Motta, J. *Molecules* **2007**, *12*, 1471 (and references therein); (b) Salerno, A.; Figueroa, M. A.; Perillo, I. A. *Synth. Commun.* **2003**, *33*, 3193.
13. (a) White, A. C.; Black, R. M. U. S. Patent 3,996,207, 1976; (b) Mirskova, A. N.; Seredkina, S. G.; Kalikhman, I. D.; Bannikova, O. B.; Voronkov, M. G. *Russ. Chem. Bull.* **1989**, *4*, 815.
14. Díaz, J. E.; Bisceglia, J. A.; Mollo, M. C.; Orelli, L. R. *Tetrahedron Lett.* **2011**, *52*, 1895 (and references cited therein).
15. Hedrera, M. E.; Salerno, A.; Lopez, J.; Niemezv, F.; Perillo, I. A. *Trends Org. Chem.* **2008**, *12*, 61.
16. (a) For reviews on microwave chemistry, see: *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (b) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 55; (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653; (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
17. *Advances in Heterocyclic Chemistry*; Katritzky, A., Ed.; Academic Press, 1988; Vol. 43.