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New synthetic route for selectively substituted 1,*n*-diamines. Synthesis of *N*-aryl tetra- and pentamethylenediamines

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ABSTRACT

A general procedure for the synthesis of *N*-aryltetra- and pentamethylenediamines **1** by acid hydrolysis of *N*-aryl-*N*′-acylalkylenediamines **2** under microwave irradiation is described. The precursors **2** are obtained by amination of the corresponding *N*-(ω-haloalkyl)benzamides with aromatic amines **3**.

1,*n*-Diamines and their derivatives have been well studied for presenting pharmacological activities common to natural polyamines[1] as well as for their usefulness as synthetic intermediates. Ethylene- and trimethylenediamines are interesting for their ability to complex metal ions,[2] whereas *N*-substituted derivatives of the higher homologs, putrescine, and cadaverine inhibit cell proliferation.[3,4] Therefore, the synthesis of selectively substituted 1,*n*-diamines represents a field of interest.

The synthesis of symmetrically substituted *N*,*N*′-dialkyl-1,*n*-diamines is relatively easy. The most common methods use the corresponding 1,*n*-diamine as a precursor and imply the derivatization of the primary amino groups by either direct alkylation with the halogenated derivatives or transformation in amides or imines and further reduction.[4] These methods cannot adapt to the preparation of *N*,*N*′-asymmetrically substituted diamines since both the amino groups in the substrate have the same reactivity. Therefore, the preparation of these compounds presents synthetic difficulties and limits the number and type of accessible derivatives, thus requiring more complex synthetic strategies. Among others, *N*-monosubstituted 1,*n*-diamines are adequate precursors for asymmetric *N*,*N*′-disubstituted derivatives. Convenient synthetic routes to *N*-alkyl- and benzyl-substituted linear diamines have already been described;[5] however, their *N*-aryl derivatives are not yet readily available.

The classical method for obtaining *N*-aryl-1,*n*-diamines starting from diamine is the aryl halide amination, which is limited to precursors with strong electron-withdrawing groups.[6–8]A variation of this method that does not require reactive aryl halides as precursors uses transition metals as catalysts, and has been particularly applied for the synthesis of *N*-aryltrimethylenediamines.[9] However, in other cases these reactions require high temperatures, and thus result in *N*,*N*′-diarylated compounds. Other multistep syntheses have been developed starting from different precursors.[10–12]

The above-mentioned methods have been generally applied to the synthesis of *N*-aryl derivatives of ethylene- and trimethylenediamine. Instead, methods for the synthesis of *N*-aryltetra- and pentamethylenediamines have been scarcely studied. A general approach for the preparation of these compounds implies the synthesis of ω-arylaminoalkanonitriles and the generation of the primary amino group by reduction of the corresponding cyano group. In 1958, this method was used to obtain *N*-phenylpentamethylenediamine[13] and, later, in 1972, Nilsson obtained *N*-*p*-tolylpentamethylenediamine, an active fibrin-stabilizing factor (FSF) inhibitor.[14] More recently, *N*-phenyltetramethylenediamine was obtained in a low yield (43%) by *N*-arylation of 1,4-diaminobutane using a dicyclopentadienyl iron complex of chlorobenzene containing phenolphthalein bridges.[15]

Our group has previously developed the synthesis of *N*-arylethylene- and trimethylenediamines by amination of 2-bromoethyl- and 3-bromopropylamine with aromatic amines.[10] However, since the necessary precursors for the preparation of the corresponding tetra- and pentamethylenediamines are not easily available, we designed an alternative synthetic route.

In this Letter, we describe a new method to obtain *N*-aryltetra- and pentamethylenediamines **1** by the hydrolysis of the corresponding *N*-aryl-*N*′-acylalkylenediamines **2** (Scheme 1) which was optimized employing microwave irradiation, a valuable technique which accelerates chemical reactions and minimizes thermal decomposition of the products.[16]

Compounds **2** were synthesized by the amination of *N*-(ω-haloalkyl)amides **3**, which provide the tetra- and pentamethylenediamine moiety. This method depends on the availability of compounds **3**, whose synthesis was optimized by von Braun degradation of *N*-acylpyrrolidine and piperidine.[17]

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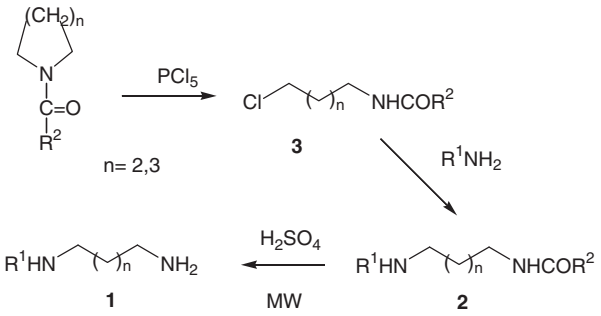

Scheme 1.

Table 1
Compounds **1** and **2** prepared

Compounds		*n*	R^1	R^2
1	**2**			
a	a	2	C_6H_5	C_6H_5
b	b	2	4-$CH_3C_6H_4$	C_6H_5
c	c	2	4-ClC_6H_4	C_6H_5
d	d	2	4-$NO_2C_6H_4$	C_6H_5
e	e	2	3,4-$Cl_2C_6H_3$	C_6H_5
f	f	3	C_6H_5	C_6H_5
g	g	3	4-$CH_3C_6H_4$	C_6H_5
h	h	3	4-ClC_6H_4	C_6H_5
i	i	3	4-$NO_2C_6H_4$	C_6H_5
j	j	3	3,4-$Cl_2C_6H_3$	C_6H_5
a	k	2	C_6H_5	2,4-$Cl_2C_6H_3$
a	l	2	C_6H_5	*ter*-C_4H_9

The aminolysis of ω-chlorobutyl(pentyl)benzamides **3** (*n* = 2, 3; $R^2 = C_6H_5$) with aromatic amines led to the expected *N*-benzoyl-*N*′-arylalkylenediamines **2a–j** (Table 1), accompanied with *N*,*N*-bis(ω-benzamidoalkyl)arylamines in variable amounts. In order to minimize the bis derivative formation, the reaction was assayed under different conditions (in toluene, without a solvent and at different temperatures), reaching the best results when heating at 100–120 °C in the absence of the solvent (yields 75–87%).[18]

Hydrolysis reactions of compounds **2a–j** were studied in acid and alkaline media heating under reflux. Using 20% aq NaOH, the reactions were not completed after 18 h of heating, and the expected *N*-arylalkylenediamines **1a–j** were obtained in low yields (20–35%) together with the starting material and tar by-products. The acid hydrolysis was tested with different concentrations of aq H_2SO_4. The best results were obtained using 50% aq H_2SO_4, affording diamines **1a–j** after 7–12.5 h of heating, although with moderate yields (36–41%) (Table 2).[19]

With the aim to enhance the reaction yields and decrease the reaction times, the acid hydrolysis was optimized using microwave irradiation. The reactions were carried out in a Reactor Microwave Digestion System WX-4000, EU chemical instruments.

The reactions required relatively high temperatures. At 110 °C (300 W), no conversion to the hydrolysis products was observed, whereas at 120–130 °C (400 W) the reactions required relatively longer times (50–60 min) resulting in low yields due to product decomposition. At 150 °C (500 W), the hydrolysis products were obtained in high yields (74–82%) leading to complete hydrolysis within 7–10 min (Table 2).

In a typical reaction, in a 10-mL glass tube were placed *N*-aryl-*N*′-acylalkylenediamines **2e** (1 mmol) and 50% aq H_2SO_4 (5 mL). The tube was closed with a septum and placed into the microwave cavity. The reaction mixture was subjected to microwave irradiation at a power 500 W (150 °C) for 7 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the reaction product **1e** was isolated as was indicated in the conventional procedure.[19]

Table 2
Conversion of **2** → **1** using 50% aq H_2SO_4

Compound		Conventional heating		Microwave irradiation (150 °C, 500 W)	
2	**1**	Time (h)	Yields (%)	Time (min)	Yields (%)
a	a	7	38	10	82
b	b	12.5	40	8	77
c	c	10	41	9	78
d	d	11	37	7	76
e	e	11	40	7	78
f	f	7.5	41	8	74
g	g	10	40	10	79
h	h	11	36	9	75
i	i	8.5	39	9	78
j	j	9.5	40	10	79
k	a	15	41	15	77
l	a	11	39	9	78

The general results indicate that irradiating the samples to a potency (500 W, 150 °C), the reaction times are dramatically reduced, from 7–12.5 h (conventional heating) to 7–15 min, the formation of the by-products is minimized, and the yields increase.

N-Arylalkylenediamines **1a–j** were obtained as oils and spectroscopically characterized by MS (EI), IR, ^1H, and ^{13}C NMR.

With the aim to determine the nature of the most appropriate acyl residue for this synthetic sequence, other two compounds **2** were assayed. Thus, *N*-pivaloyl and *N*-2,4-dichlorobenzoyl derivatives **2k,l** (Table 1) were synthesized and subjected to acid hydrolysis. We observed that the times required for the hydrolysis and the yields obtained did not present advantages over the benzoyl derivative (Table 2).

The main limitation of the method was observed in the case of aryl groups having acid-labile substituents. Thus, the hydrolysis of alkoxyphenyl derivatives **2** (R^1 = 4-$CH_3OC_6H_4$, 3,4,5-$(CH_3O)_3C_6H_2$; $R^2 = C_6H_5$; *n* = 2, 3) afforded a complex mixture of non-identified products. On the other hand, the method can be used for compounds with aryl groups containing substituents susceptible to reduction, such as halogens and nitro. This represents an advantage with respect to the method previously described in the literature,[12,13] in which the primary amine is generated by the reduction of the cyano group.

In conclusion, we report a novel synthetic approach for the synthesis of *N*-aryltetra- and pentamethylenediamines **1** of biological and biomedical interest by acid hydrolysis of *N*-aryl-*N*′-acylalkylenediamines **2**. We have also shown that microwave irradiation is essential for fast, clean, and high-yielding reactions.

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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.2010.07.075.

References and notes

1. (a) Callery, P. S.; Egorin, M. J.; Li, Y.; Yuan, Z. M. U.S. Patent 5612,329, 1997; *Chem. Abstr.* **1997**, *126*, 238254; (b) Frydman, B. PCT Int. Appl. WO 96,40,096, 1996; *Chem. Abstr.* **1997**, *126*, 126897m; (c) Frydmann, B.; Valasinas, A. *Exp. Opin. Ther. Patents* **1999**, *9*, 1055.
2. Among others: (a) Gust, R.; Burgemeister, T.; Mannchreck, A. *J. Med. Chem.* **1990**, *33*, 2535; (b) Brunner, H.; Hankofer, P.; Hoizinger, U.; Treittinger, B.; Schonenberger, H. *Eur. J. Med. Chem.* **1990**, *25*, 35.

3. Aizencang, G.; Harari, P.; Buldain, G.; Guerra, L.; Pickart, M.; Hernandez, P.; Frydman, B. *Cell. Mol. Biol.* **1998**, *44*, 615.
4. Among others: (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) Burns, M. R. U.S. 6872,852, 2005.
5. Among others: (a) Salvatore, R. N.; Schmidt, S. E.; Shin, S., II; Nagle, A. S.; Worrell, J. H.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 9705; (b) Cesar, E. T.; Berg, R. N.; Fontes, A. P. S.; Silva, H.; Saraiva, M. F.; Guerra, W.; de Almeida, M. V. *Bull. Korean Chem. Soc.* **2007**, *28*, 295; (c) da costa, C. F.; Coimbra, E. S.; Braga, F. G.; dos Reis, R. C. N.; da Silva, A. D.; de Almeida, M. V. *Biomed. Pharmacother.* **2009**, *63*, 40; (d) Alonso Garrido, D. O.; Buldain, G.; Frydman, B. *J. Org. Chem.* **1984**, *49*, 2021. and references therein.
6. (a) Perillo, I. A.; Fernández, B.; Lamdan, S. *Journal. Chem. Soc., Perkin Trans. 2* **1977**, 2068; (b) Gavish, M.; Dwek, R. A.; Givol, D. *Biochemistry* **1977**, *16*, 3154; (c) Perillo, I. A.; Lamdan, S. *J. Heterocycl. Chem.* **1973**, *10*, 915.
7. Beletskaya, I. P.; Artamkina, G. A.; Ivushkin, V. A.; Guilard, R. *Tetrahedron Lett.* **2000**, *41*, 313.
8. Delcros, J.-G.; Tomasi, S.; Duhieu, S.; Foucault, M.; Martín, B.; Le Roch, M.; Eifler-Lima, V.; Renault; Úrica, P. *J. Med. Chem.* **2006**, *49*, 232.
9. (a) Beletskaya, I. P.; Bessmertnykh, A. G.; Averin, A. D.; Denat, F.; Guilard, R. *Eur. J. Org. Chem.* **2005**, 261; (b) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1997**, *38*, 2287; (c) Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997.
10. (a) Perillo, I.; Caterina, M. C.; Lopez, J.; Salerno, A. *Synthesis* **2004**, 851; (b) Orelli, L. R.; García, M. B.; Niemevz, F.; Perillo, I. A. *Synth. Commun.* **1999**, *29*, 1819.
11. (a) Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 6257; (b) Kesten, S. R.; Heffner, T. G.; Johnson, S. J.; Pugley, T. A.; Wright, J. L.; Wise, L. D. *J. Med. Chem.* **1999**, *42*, 3718.
12. Maillard, M. C.; Perlman, M. E.; Amitay, O.; Baxter, D.; Berlove, D.; Connaughton, S.; Fischer, J. B.; Guo, J. Q.; Hu, L.-Y.; McBurney, R. N.; Nagy, V.; Subbarao, K.; Yost, E. A.; Zhang, L.; Durant, G. *J. Med. Chem.* **1998**, *41*, 3048.
13. Gassenmeier, E.; Hrubesch, A. Badische Anilin- & Soda-Fabrik Akt. Ger. 1953, 875,523; *Chem. Abs.* **1958**, *52*, 12897h.
14. Stenberg, P.; Nilsson, L. G. *J. Med. Chem.* **1972**, *15*, 674.
15. Aziz, A.-E.; Bernardin, S. A.; Tran, K. *Tetrahedron Lett.* **1999**, *40*, 1835.
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. Disc.* **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. Hedrera, M.; Salerno, A.; Lopez, J.; Niemevz, F.; Perillo, I. A. *Trends Org. Chem.* **2008**, *12*, 61.
18. *General procedure for synthesis of compounds* **2**: A mixture of the appropriate *N*-(ω-chloroalkyl)benzamide **3** (0.02 mol) and the corresponding arylamine (0.04 mol) was heated for 1 h under reflux in an oil bath at 120 °C. After cooling, the crude material was treated with hot water (10 mL) in order to extract the arylamine hydrochloride, and then heated for 5 minutes with 10% HCl (10 mL) and filtered before cooling. The filtrate was alkalinized with 10% NaOH to *p*H 14. The product was filtered, dried, and recrystallized from cyclohexane.
19. *General procedure for the under conventional heating synthesis of N-aryltetra(penta)methylenediamines* **1**. A solution of the appropriated *N*-aryl-*N*′-acylalkylenediamine (**2**) (1 mmol) in 50% P/V aqueous H_2SO_4 (15 mL) was heated at reflux for 7–13 h and monitored by TLC. When the reaction was completed, the solution was made alkaline with 50% aqueous NaOH in an ice bath and extracted with methylene chloride (3×5 mL). The organic layers were pooled, washed with water, dried, and evaporated in vacuo affording the corresponding compounds **1** as oils which were purified by column chromatography (chloroform/methanol 8:2 to 1:1).