Tetrahedron Letters 52 (2011) 5238–5240

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

1,*n*-Diamines. Part 3: Microwave-assisted synthesis of *N*-acyl-*N*′-arylhexahydropyrimidines and hexahydro-1,3-diazepines

Juan Á. Bisceglia, Jimena E. Díaz, Romina A. Torres, Liliana R. Orelli *

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

ARTICLE INFO

Article history:
Received 5 July 2011
Revised 23 July 2011
Accepted 27 July 2011
Available online 5 August 2011

Keywords:
Polyamine analogs
Cyclic aminals
N-Formylations
Cyclocondensation
Microwaves

ABSTRACT

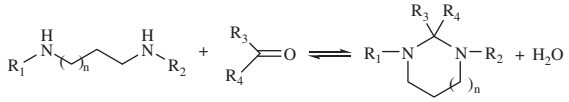
In this Letter we present a method for the synthesis of *N*-acyl-*N*′-arylhexahydropyrimidines **1**, by ring closure of *N*-acyl-*N*′-aryl-1,3-propanediamines **3** with formaldehyde. Cyclodehydrations were performed in aqueous medium under microwave irradiation, and led to high yields of the desired compounds in remarkably short reaction times. The method also allowed for the synthesis of hitherto unreported *N*-acyl-*N*′-arylhexahydro-1,3-diazepines **2**. The acyclic tetramethylenic precursors **4** were synthesized by selective functionalization of *N*-arylputrescines.

Introduction

Cyclic aminals are compounds of interest due to their pharmacological and chemical properties. The five membered heterocyclic aminal (imidazolidine) core is found in many bioactive compounds like antiinflammatory and analgesic agents,[1] fungicides, antibacterials, parasiticides, and antivirals.[1,2] Six membered cyclic aminals (hexahydropyrimidines) are also present in biologically active compounds, acting as analgesics, parasiticides,[3] antifungals, and antibacterials.[4] Besides, hexahydropyrimidines also behave as prodrugs of pharmacologically active di[5] and polyamines.[6] Such compounds have recently been applied as pro-perfumes, in the controlled release of volatile aldehydes and ketones.[7] In synthetic organic chemistry, cyclic aminals are useful as protecting groups in the selective functionalization of di and polyamines and also in organocatalytic reactions[8] or as auxiliaries in asymmetric synthesis.[9] Due to their biological and chemical properties, imidazolidines and hexahydropyrimidines have received a great deal of attention. Their higher homologs (hexahydro-1,3-diazepines) have been less studied, maybe due to the intrinsical difficulty of ring closure reactions leading to seven-membered cyclic aminals.[10]

The synthetic precursors of *N*-acyl-*N*′-arylimidazolidines or hexahydropyrimidines, namely *N*-acyl-*N*′-aryldi (or tri)methylenediamines, are prepared by acylation of the corresponding *N*-(ω-bromoalkyl) amine followed by aminolysis.[11] This strategy is not suitable for tetramethylenediamine derivatives, which can alternatively be synthesized by *N*-monoacylation of *N*-arylputrescines.[12] Selectively N-substituted 1,4-diaminobutanes are of biochemical and pharmacological interest as synthetic analogs of the natural polyamine putrescine. Several derivatives of the parent diamine have been studied as antibiotics, antineoplastics, antiparasitic agents, and NMDA or cholinergic modulators.[13] On the other hand, some biologically active 1,3-propanediamine derivatives have also been reported.[14] In previous work, we developed a two-step synthesis of *N*-arylputrescines, by aminolysis of 4-chlorobutyronitrile followed by reduction.[15] Further functionalization of such intermediates led to novel acyclic and heterocyclic *N*-arylputrescine derivatives.[12] In the context of our research on nitrogen heterocycles,[12,16] we were interested in tertiary amides derived from six and seven membered cyclic aminals (hexahydropyrimidines and hexahydro-1,3-diazepines, respectively). The classical method for the preparation of aminals involves condensation of a diamine with an aldehyde or ketone (Scheme 1), and requires the use of different drying agents[17] or the azeotropic distillation of water,[18] in order to shift the equilibrium toward the products.

In a recent report, the synthesis of *N*-acyl-*N*′-arylimidazolidines was achieved in the presence of activated Montmorillonite K-10 in THF under microwave irradiation in a domestic oven.[2] An interesting



Scheme 1. Condensation reaction leading to cyclic aminals.

* Corresponding author. Tel./fax: +54 11 4964 8250.
E-mail addresses: lorelli@ffyb.uba.ar, von_orelli@yahoo.com (L.R. Orelli).

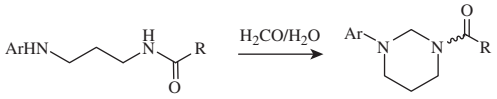
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.131

method for the synthesis of acyclic and heterocyclic aminals was developed by Jurcik et al., which involves heating the reactants in water for several (3–16) hours.[19] The reported examples, however, only include six and seven-membered heterocycles bearing *N*-alkyl substituents. The lower nucleophilicity of the arylamino as well as the amido groups of compounds **3** and **4** could, in principle, become a limiting factor for the synthesis of the corresponding cyclic aminals.

Although organic reactions on water are well known, they are receiving increasing attention in the last years.[20] On the other hand, reactions performed under microwave irradiation proceed in general faster, more cleanly, and with higher yields than with conventional heating.[21] The possibility of performing organic reactions in water under microwave irradiation combines the benefits of short reaction times, easy work-up procedures and the use of a clean solvent with highly efficient energy transfer.[22] These features prompted us to investigate the microwave-assisted synthesis of compounds **1** and **2** in water and without catalysts.

Results and discussion

We examined first the reaction between *N*-(4-chlorophenyl)-*N*′-formyl-1,3-propanediamine (**3a**) and excess formaldehyde (38% in water) at room temperature, using methanol as the solvent on the basis of previous work.[4,23] In such conditions, the reaction was completed in 12 h (69%), while heating for 6 h at reflux temperature lead to lower yield (51%) of the expected product. Cyclization led to 67% yield when performed in the same solvent, under microwave irradiation in a single mode reactor (5 min at 70 °C). Bearing in mind a recent report on the synthesis of aminals in aqueous medium,[19] the condensation was attempted by treatment of the substrate with aqueous formaldehyde under microwave irradiation (Scheme 2). In such conditions, total disappearance of the substrate was achieved in only 1 min at 110 °C yielding 87% of compound **1a** (Table 1). Encouraged by these results, several substrates with increasing steric hindrance in the amide moiety were reacted in the same conditions.[24] In all cases, the corresponding cyclic aminals were isolated in good to high yields as the only product (Table 1). An exception was *N*-pivaloyl-*N*′-(4-chlorophenyl)- 1,3-propanediamine, which did not react even after longer reaction times (5 min at 110 °C). The method was successful both for aminoamides with electron releasing or moderately electronegative substituents on the aryl moiety. Interestingly, derivatives **1i**,**n** bearing sterically hindering substituents in the aryl moiety were also synthesized with high yields (Table 1). In all cases, compounds **1** were obtained as inseparable mixtures of *E*/*Z* diastereoisomers due to hindered rotation about the (O)C–N bond.[16g]



Scheme 2. Synthesis of *N*-acyl-*N*′-arylhexahydropyrimidines **1**.

Table 1
Synthesis of *N*-acyl-*N*′-arylhexahydropyrimidines **1a–n**

Compound **1**	Ar	R	Yield[a,b] (%)	Yield[a,c] (%)
a	4-ClC_6H_4	H	69[d]	87
b	4-ClC_6H_4	CH_3	64[d]	85
c	4-ClC_6H_4	C_2H_5	61[d]	80
d	4-ClC_6H_4	*iso*-C_3H_7	16[d]	70
e	4-ClC_6H_4	C_6H_5	68[d]	95
f	C_6H_5	H	64[d]	93
g	C_6H_5	CH_3	63[d]	90
h	4-$CH_3OC_6H_4$	CH_3	49[d]	73
i	2-ClC_6H_4	CH_3	71[d]	95
j	4-FC_6H_4	H	ND	79
k	4-$CH_3C_6H_4$	CH_3	ND	79
l	C_6H_5	C_2H_5	ND	89
m	4-FC_6H_4	*iso*-C_3H_7	ND	66
n	2,6-$(CH_3)_2C_6H_3$	CH_3	ND	78

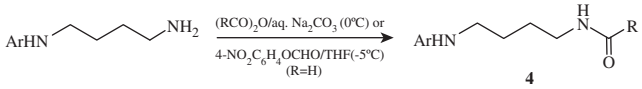
[a] Yields correspond to pure compounds.
[B] rt, 12–24 h.
[c] μW heating.
[d] Ref. 16g.

Examination of the experimental results indicates that microwave irradiation per se has the expected effects of reaction rate acceleration. However, the aqueous medium is also important in order to achieve optimum yields of the desired products in short reaction times. This is quite surprising taking into account that the reaction is reversible and proceeds with the liberation of a stoichiometric amount of water (Scheme 1). The combined effect of microwaves and aqueous reaction medium is more striking in the case of the less reactive isobutyramide **1d**.

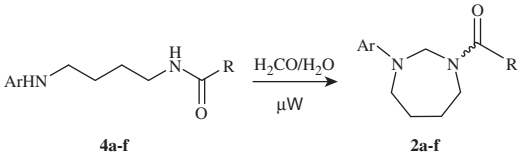
In view of these encouraging results, we attempted next the synthesis of the homologous seven-membered cyclic aminals (Scheme 4), which were not described in the literature. Such compounds are of particular interest as synthetic analogs of the natural polyamine putrescine. The acyclic precursors (*N*-acyl-*N*′-arylputrescines **4**) were synthesized by selective N-acylation of *N*-arylputrescines with carboxylic acid anhydrides (Scheme 3).[12]

Selective formylation of *N*-(4-chlorophenyl)putrescine was achieved employing 4-nitrophenyl formate in THF, and showed complete selectivity toward the primary amino group (Scheme 3).

Cyclodehydration of aminoamide **4a** with aqueous formaldehyde in methanol did not take place at room temperature (24 h) The microwave assisted reaction in aqueous medium, in contrast, was completed in 2 min at 110 °C (Scheme 4). In such conditions,[24]



Scheme 3. Selective acylation of *N*-arylputrescines.



Scheme 4. Synthesis of *N*-acyl-*N*′-arylhexahydro-1,3-diazepines **2**.

Table 2
Microwave-assisted synthesis of *N*-acyl-*N*′-arylhexahydro-1,3-diazepines **2a–f**

Compound **2**[a]	Ar	R	Yield[b] (%)
a	4-ClC_6H_4	H	79
b	4-ClC_6H_4	CH_3	84
c	4-ClC_6H_4	C_2H_5	50
d	4-ClC_6H_4	C_6H_5	71
e	C_6H_5	CH_3	77
f	4-$CH_3C_6H_4$	C_6H_5	70

[a] Compounds **2a–f** were obtained as inseparable mixtures of *E*/*Z* diastereoisomers.
[b] Yields correspond to pure compounds.

aminoamides **4b–f** afforded the corresponding cyclic aminals **2b–f** as the only product in good yields (Table 2). The reaction is sensitive to steric hindrance both in the aryl and carbonyl groups. In fact, *N*-isobutyryl-*N*′-(4-chlorophenyl)putrescine and *N*-acyl-*N*′-(2-methylphenyl)putrescine did not react even in forcing conditions (5 min at 120 °C). Analogous results were obtained when *N*-benzoyl-*N*′-(4-chlorophenyl)-1,5-pentanediamine[12] was treated with formaldehyde in the same conditions.

Conclusions

In conclusion, we have developed an efficient synthesis of *N*-acyl-*N*′-arylhexahydropyrimidines, by microwave-assisted cyclodehydration of the corresponding aminoamides in aqueous medium in the absence of catalysts. Hexahydropyrimidines bearing substituents of variable stereoelectronic nature were obtained with high yields in short reaction times. The procedure also allowed for the synthesis of hitherto unreported *N*-acyl-*N*′-arylhexahydro-1,3-diazepines, which are potentially bioactive compounds as synthetic analogs of the natural polyamine putrescine. To our knowledge, this is the first report on such compounds in the literature.

Acknowledgments

This work was supported by the University of Buenos Aires and by the CONICET. We are also grateful to María C. Mollo (MS) and to Lic. Gastón Estruch (SANICO Argentina) for technical collaboration.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.131.

References and notes

1. Sharma, V.; Khan, M. S. Y. *Eur. J. Med. Chem.* **2001**, *36*, 651–658.
2. Caterina, M. C.; Corona, M. V.; Perillo, I.; Salerno, A. *Heterocycles* **2009**, *78*, 771–781. and references therein.
3. (a) Khan, M. S.; Gupta, M. *Pharmazie* **2002**, *57*, 377–383; (b) Kalyanam, M.; Parthasarathy, P. C.; Ananthan, I.; Manyunatha, S. G.; Likhate, M. A. *Indian J. Chem., Sect B* **1992**, *31*, 243–247; (c) Vanelle, P.; Maldonado, J.; Crozet, M. P.; Senouki, K.; Delmas, F.; Gasquet, M.; Timon-David, P. *Eur J. Med. Chem.* **1991**, *26*, 709–714.
4. Bisceglia, J. A.; García, M. B.; Massa, R.; Magri, M. L.; Zani, M.; Gutkind, G. O.; Orelli, L. R. *J. Heterocycl. Chem.* **2004**, *41*, 85–90.
5. (a) Billman, J.; Khan, M. *J. Med. Chem.* **1968**, *11*, 312–314; (b) Chang, Y. H.; Evanenga, G. R.; McLamore, W. M. U.S. Patent 3 729 564; *Chem. Abstr.* **1974**, *79*, 18762.
6. (a) Golding, B. T.; Nassereddin, I. K. *J. Chem. Soc.* **1985**, 2011–2015; (b) Bergeron, R. J.; Seligsohn, H. W. *Bioorg. Chem.* **1986**, *14*, 345–355.
7. (a) Herrmann, A.; Godin, G.; Lehn, J.-M. WO 093272, 2008.; (b) Herrmann, A. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 5836–5863; (c) Godin, G.; Levrand, B.; Trachsel, A.; Lehn, J.-M.; Herrmann, A. *Chem. Commun.* **2010**, *46*, 3125–3127; (d) Buchs, B.; Godin, G.; Trachsel, A.; de Saint Laumer, J.-Y.; Lehn, J.-M.; Herrmann, A. *Eur. J. Org. Chem.* **2011**, 681–695.
8. Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147–1168.
9. (a) Alexakis, A.; Mangeney, P.; Lensen, N.; Tranchier, J. P.; Gosmini, R.; Raussou, S. *Pure Appl. Chem.* **1996**, *68*, 531–534; (b) Denmark, S. E.; Stadler, H.; Dorow, R. L.; Kim, J.-H. *J. Org. Chem.* **1991**, *56*, 5063–5079; (c) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556–2558; (d) Clayden, J.; Lai, L. W.; Helliwell, M. *Tetrahedron* **2004**, *60*, 4399–4412.
10. Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Soc., PT2* **1997**, 169–171.
11. Orelli, L. R.; Niemevz, F.; García, M. B.; Perillo, I. A. *J. Heterocycl. Chem.* **1999**, *36*, 105–112. and references therein.
12. Díaz, J. E.; Bisceglia, J. A.; Mollo, M. C.; Orelli, L. R. *Tetrahedron Lett.* **2011**, *52*, 1895–1897.
13. (a) Frydman, B.; Valasinas, A. *Exp. Opin. Ther. Patents* **1999**, *9*, 1055–1068; (b) Aizencang, G.; Harari, P.; Buldain, G.; Guerra, L.; Pickart, M.; Hernández, P.; Frydman, B. *Cell. Mol. Biol.* **1998**, *44*, 615–625; (c) Burns, M. R. U.S. Patent 2005 6,872,852.; (d) Sacaan, A. I.; Johnson, K. M. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1060–1063; (e) McGurk, J. F.; Bennett, M. V. L.; Zukin, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9971–9974; (f) Bigge, C. F.; Malone, T. C. *Exp. Opin. Ther. Patents* **1993**, *3*, 951–989; (g) Bergeron, R. J.; Yao, G. W.; Yao, H.; Weimar, W. R.; Sninski, C. A.; Raisler, B.; Feng, Y.; Wu, Q.; Gao, F. *J. Med. Chem.* **1996**, *39*, 2461–2471.
14. (a) Rehse, K.; Carstensen, A.; Ernst, H. *J. Arch. Pharm.* **1987**, *320*, 829–836; (b) Murata, Y.; Miyamoto, E.; Ueda, M. *Yakuzaigaku* **1989**, *49*, 327–330; (c) Murata, Y.; Miyamoto, E.; Kawashima, S. *Caries Res.* **1990**, *24*, 254–255.
15. Link, N. P.; Díaz, J. E.; Orelli, L. R. *Synlett* **2009**, 751–754.
16. (a) García, M. B.; Grilli, S.; Lunazzi, l.; Mazzanti, A.; Orelli, L. *J. Org. Chem.* **2001**, *66*, 6679–6684; (b) García, M. B.; Grilli, S.; Lunazzi, l.; Mazzanti, A.; Orelli, L. *Eur. J. Org. Chem.* **2002**, *23*, 4018–4023; (c) García, M. B.; Orelli, L. R.; Magri, M. L.; Perillo, I. A. *Synthesis* **2002**, *23*, 2687–2690; (d) Magri, M. L.; Vanthuyne, N.; Roussel, C.; García, M. B.; Orelli, L. R. *J. Chromatogr., A* **2005**, *1069*, 203–208; (e) Orelli, L. R.; García, M. B.; Perillo, I. A.; Tonidandel, L.; Traldi, P. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 823–828; (f) Lavaggi, M. L.; Aguirre, G.; Boiani, L.; Orelli, L. R.; García, M. B.; Cerecetto, H.; González, M. *Eur. J. Med. Chem.* **2008**, *43*, 1737–1741; (g) Bisceglia, J. A.; Mollo, M. C.; Orelli, L. R. *J. Mol. Struct.* **2010**, *966*, 79–84; (h) Díaz, J. E.; García, M. B.; Orelli, L. R. *J. Mol. Struct.* **2010**, *982*, 50–56.
17. (a) Liebermann, S. V. *J. Am. Chem. Soc.* **1955**, *77*, 1114–1116; (b) Kerfanto, M.; Brault, A.; Venien, F.; Morvan, J. M.; LeRouzic, A. *Bull. Soc. Chem. Fr.* **1975**, 196–200; (c) Sekiya, M.; Sakai, H. *Chem. Pharm. Bull.* **1969**, *17*, 32–39.
18. Stewart, A. T.; Hauser, C. R. *J. Am. Chem. Soc.* **1955**, *77*, 1098–1103.
19. Jurcik, V.; Wilhelm, R. *Tetrahedron* **2004**, *60*, 3205–3210.
20. Chanda, A.; Forkin, V. *Chem. Rev.* **2009**, *109*, 725–748.
21. (a) Among others: *Microwaves in Organic Synthesis.* Loupy, A., Ed.; Wiley-VCH: Winheim, 2002.; (b) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Disc.* **2006**, *5*, 51–63; (c) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (d) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. *Drug Discovery Today: Technol.* **2005**, *2*, 155–161; (e) Leadbeater, N. B. *Chem. Commun.* **2005**, 2881–2902; (f) Lindström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (g) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (h) Caddick, S. *Tetrahedron* **2005**, *51*, 10403–10432; (i) Kappe, C. O.; Dallinger, D. *Mol. Diversity* **2009**, *13*, 71–193; (j) Van der Eicken, E.; Kappe, C. O. *Microwave-assisted synthesis of heterocycles*; Springer: Distribution Center, GmbH, 2006.
22. Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
23. Perillo, I. A.; García, M. B.; Bisceglia, J. A.; Orelli, L. R. *J. Heterocycl. Chem.* **2002**, *39*, 655–661.
24. General procedure for the synthesis of compounds **1** and **2**: The corresponding aminoamide (1 mmol) was treated with aqueous formaldehyde (3 mL). The mixture was irradiated in a microwave reactor (Monowave 300, Anton Paar) for 1 min (compounds **3a–n**) or 2 min (compounds **4a–f**) at 110 °C, in a closed vessel with stirring. The reaction mixture was then treated with a mixture of dichloromethane (20 mL) and saturated aqueous Na_2CO_3 (5 ml). The aqueous phase was extracted with dichloromethane (4 × 20 mL). The organic phases were pooled, washed with water, treated with anhydrous Na_2SO_4 and filtered. The solvent was eliminated in vacuo. The crude products were purified by flash column chromatography (Silica Gel, *n*-hexane/dichloromethane/ethyl acetate 15:85:0 to 0:95:5).