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1,*n*-Diamines. Part 2: Synthesis of acyclic and heterocyclic *N*-arylputrescine derivatives

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ABSTRACT

In the present Letter we report the use of *N*-arylputrescines as synthetic intermediates for the preparation of *N*-acyl-*N*′-aryltetramethylenediamines **3** and related seven-membered heterocyclic amidines **4**. Compounds **1** were synthesized by Cs_2CO_3/KI-mediated aminolysis of 4-chlorobutyronitrile and subsequent reduction. N-Acylation of diamines **1** with carboxylic acid anhydrides led selectively to *N*-acyl-*N*′-aryl tetramethylenediamines **3**. Microwave-assisted ring closure of such precursors promoted by PPE allowed for the synthesis of hitherto unreported 1-aryl-2-alkyl-1*H*-1,4,5,6-tetrahydro-1,3-diazepines **4**.

1. Introduction

Cyclic amidines represent a heterocyclic core of wide pharmacological interest. Among them, dihydroimidazoles[1] and tetrahydropyrimidines[2] are found in many biologically active compounds. Due to their broad spectrum of biological activity, such heterocycles have received a great deal of attention in connection to their synthesis. In contrast, only scattered references on seven-membered cyclic amidines (tetrahydrodiazepines) are available in the literature. Tetrahydro-1,3-diazepines have been studied owing to the biological properties of some members, acting as diuretics, hypoglycemiants, anti-inflammatory, and antispasmodics.[3] More recently, some tetrahydro-1,3-diazepines have been investigated as NMDA receptor antagonists[4] and dopamine D4 receptor[1b] or muscarinic agonists.[5] The described syntheses of 2-alkyl-1*H*-4,5,6,7-1,3-diazepines involve the reaction of 1,4-butanediamine with carboxylic acids and their derivatives.[3a–c,6] Due to the considerably lower nucleophilicity of the arylamino group, application of such procedures to *N*-aryl derivatives would involve drastic reaction conditions, which may result in decomposition of sensitive substrates. Polyphosphoric acid esters are mild irreversible dehydrating reagents of the Lewis acid type that activate oxygen and nitrogen functionalities toward nucleophilic attack and, at the same time, react chemically with water. Ethyl polyphosphate (PPE) and trimethylsilylpolyphosphate (PPSE) have been used as dehydrating agents for the synthesis of *N*-aryl five- to eight-membered cyclic amidines.[7]

Reactions performed under microwave irradiation proceed in general faster, more cleanly, and with higher yields than with conventional heating.[8] Cyclocondensation is one of the most important methods for the synthesis of heterocycles, and microwave heating has found interesting applications in this area.[9] In previous work, we investigated the use of microwave irradiation to enhance the PPE-promoted synthesis of cyclic amidines.[10]

The synthetic precursors of *N*-aryldihydroimidazoles or tetrahydropyrimidines, namely *N*-acyl-*N*′-aryldi (or tri)methylenediamines, are prepared by acylation of the corresponding *N*-(ω-bromoalkyl)amine followed by aminolysis.[7a,c] This strategy is not suitable for tetramethylenediamine derivatives, which can alternatively be synthesized by von Braun reaction of *N*-acylpyrrolidines with PCl_5 followed by aminolysis.[7c] The overall yields of this method are moderate, and the limiting step is the synthesis of the precursor *N*-(4-chloroalkyl)amides.[11] An additional important drawback is that the procedure is restricted to *N*-acyl derivatives without α-hydrogens. Thus, *N*-aryl-*N*′-acyltetramethylenediamines bearing primary or secondary alkyl substituents in the acyl moiety are not available through this methodology. In this context, selective N-acylation of *N*-arylputrescines **1** seemed an interesting alternative for the preparation of compounds **3**.

Selectively N-substituted 1,4-diaminobutanes are of biochemical and pharmacological interest as synthetic analogs of the natural polyamine putrescine. Several derivatives have been described acting as antibiotics, antineoplastics, antiparasitic agents, and NMDA or cholinergic modulators.[12] In the context of our research on

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nitrogen compounds,[13] N-substituted putrescines represent suitable precursors of selectively N,N′-disubstituted tetramethylenediamines and related heterocycles.

2. Results and discussion

In a previous publication we presented some preliminary results on the synthesis of diamines **1**.[14] An alternative multistep synthesis was recently reported,[15] although it leads to comparatively lower global yields of the diamines and it relies on *N*-(4-chloroalkyl)amides as the precursors. In the present work, *N*-arylputrescines **1** were thus syntesized by aminolysis of 4-chlorobutyronitrile with arylamines followed by reduction (Scheme 1).

The first step involves cesium carbonate-mediated alkylation of anilines with 4-chlorobutyronitrile in the presence of potassium iodide, and shows remarkable selectivity toward the N-monosubstituted products **2**. The whole sequence afforded the desired diamines in good to high yields (Table 1).

Aminoamides **3** were synthesized by selective monoacylation of precursors **1** (Scheme 2).

Amine acylation in Schotten–Baumann conditions is usually regarded as a click chemistry reaction.[16] Such procedure, however, may lead to diacylation by-products for substrates containing additional OH, SH, or NHR groups. Thus, specific acylating agents or catalysts have been developed for aminoalcohols and aminothiols.[17]

Acylation of compound **1a** was examined under different experimental conditions. Reaction with propionyl chloride led to the corresponding *N*,*N*′-diacyl derivative as the main product, both at rt or at −5 °C. In order to improve the selectivity toward the primary amino group, the less reactive propionic anhydride was employed as the acylating agent. At rt, the main product was the expected *N*-(4-chlorophenyl)-*N*′-propionyl derivative **3a**, accompanied by some diacylation product. Selective N-monoacylation was achieved working at 0 °C in a biphasic system (Cl_3CH/aqueous Na_2CO_3). Employing the optimized reaction conditions, we synthesized compounds **3b**–**j** in good to excellent yields and with complete selectivity (Table 2).

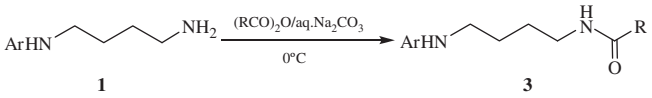
Cyclodehydration reactions leading to seven-membered cyclic amidines usually require prolonged reaction times and/or drastic conditions under conventional heating.[7c] Microwave irradiation in a domestic oven under reflux drastically reduces the reaction times.[10] The use of such instruments, however, suffers from several drawbacks regarding safety and reproducibility of the experimental results. In this work we have, therefore, used a Monowave 300 monomode reactor. Cyclodehydration of *N*-aryl-*N*′-acyl-1,4-butanediamines **3a**–**c**, **e**–**g**, **i**, **j** with a chloroformic solution of PPE (Scheme 3) was carried out in a closed vessel. The reactions were completed in 8 min at 100 °C. Isolated yields are shown in Table 3.

In order to extend the scope of the method, we synthesized by the same procedure a pentamethylenic substrate, namely *N*-isobutyryl-*N*′-(4-methylphenyl)-1,5-pentanediamine **3k**. To our knowledge, very few references on hexahydro-1,3-diazocines are reported in the literature,[10,18] and their synthesis under conventional heating involves even more drastic conditions than for the seven-membered homologs. In fact, treatment of compound **3k** with PPE under microwave irradiation (8 min at 100 °C) led to low percentual conversion to 1-(4-methylphenyl)-2-isopropyl-1,4,5,6,7,8-hexahydro-1,3-diazocine **4k** (Table 3). Longer reaction times (20 min) or higher temperatures (125 °C) did not improve the yield and resulted in partial decomposition of the reagent and development of high pressure within the reaction vessel.

Table 1
Synthesis of *N*-arylputrescines **1** via Scheme 1

Compound **1**	Ar	Yield[a] (% **2**)	Yield[a] (% **1**)
a	4-ClC_6H_4	72	87
e	4-$CH_3C_6H_4$	94	81
i	4-BrC_6H_4	62	83
j	4-FC_6H_4	66	82

[a] Yields correspond to pure compounds.



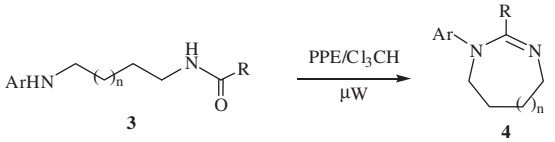
1 3

Scheme 2.

Table 2
Synthesis of compounds **3** via Scheme 2

Compound **3**	Ar	R	Yield[a] (%)
a	4-ClC_6H_4	C_2H_5	91
b	4-ClC_6H_4	CH_3	quant
c	4-ClC_6H_4	*iso*-C_3H_7	80
d	4-ClC_6H_4	C_6H_5	quant
e	4-$CH_3C_6H_4$	CH_3	quant
f	4-$CH_3C_6H_4$	C_2H_5	93
g	4-$CH_3C_6H_4$	*iso*-C_3H_7	quant
h	4-$CH_3C_6H_4$	C_6H_5	quant
i	4-BrC_6H_4	*iso*-C_3H_7	81
j	4-FC_6H_4	*iso*-C_3H_7	quant

[a] Yields correspond to pure compounds.



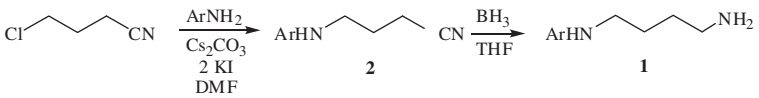
3 4

Scheme 3.

Table 3
Synthesis of compounds **4** via Scheme 3

Compound **4**	*n*	Ar	R	Yield[a] (%)
a	1	4-ClC_6H_4	C_2H_5	79
b	1	4-ClC_6H_4	CH_3	85
c	1	4-ClC_6H_4	*iso*-C_3H_7	75
e	1	4-$CH_3C_6H_4$	CH_3	87
f	1	4-$CH_3C_6H_4$	C_2H_5	71
g	1	4-$CH_3C_6H_4$	*iso*-C_3H_7	90
i	1	4-BrC_6H_4	*iso*-C_3H_7	72
j	1	4-FC_6H_4	*iso*-C_3H_7	63
k	2	4-$CH_3C_6H_4$	*iso*-C_3H_7	42

[a] Yields correspond to pure compounds.



2 1

Scheme 1.

3. Conclusions

In conclusion, we have developed a synthetic route to tetramethylenic *N*-aryl aminoamides **3** and amidines **4**, structurally related to the natural polyamine putrescine. Such compounds are potentially bioactive, and some of them are useful synthetic precursors of selectively N,N′-substituted 1,4-butanediamines.[19] The proposed method employs *N*-arylputrescines **1** as key synthetic intermediates, and represents an advantageous alternative to previously described procedures considering yields and number of steps. Besides, it can be applied for the synthesis of derivatives with primary and secondary alkyl substituents, not accessible through the literature method.

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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.2011.02.042.

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