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1,*n*-Diamines. Part 4: synthesis of 1-aryl-2-alkyl-1,4,5,6,7,8-hexahydro-1,3-diazocines

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ABSTRACT

In this Letter we present the synthesis of hitherto unreported 1-aryl-2-alkyl-1,4,5,6,7,8-hexahydro-1,3-diazocines **1**. Cyclic amidines **1** were synthesized by PPSE promoted ring closure of *N*-acyl-*N*′-arylpentamethylenediamines **2**. The cyclodehydration reaction was performed under microwave irradiation in solvent-free conditions. Precursors **2** were prepared by selective functionalization of *N*-arylcadaverines **3**.

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. Tetrahydro-1,3-diazepines have been studied owing to the biological properties of some members, acting as diuretics, hypoglycemiants, anti-inflammatories, and antispasmodics.[3] More recently, some derivatives have been investigated as NMDA antagonists[4] and dopamine D4[1b] or muscarinic agonists.[5] Literature data on the higher homologs, namely 1,4,5,6,7,8-hexahydro-1,3-diazocines, are very scarce. This may be due to the intrinsic difficulties in ring closure reactions leading to medium size heterocycles.[6] Mirskova et al. reported the reaction of cadaverine with alkylthiochloroacetylenes leading to 2-alkylthiochloromethyl-hexahydro-1,3-diazocines.[7] Other literature examples involve treatment of the parent diamine or its *N*-alkyl derivatives with carboxylic acids or their derivatives.[8] 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 the decomposition of sensitive substrates.

Perillo et al. reported the cyclodehydration of *N*-(4-nitrophenyl)-*N*′-aroyl-1,5-diaminopentanes to the corresponding hexahydrodiazocines by conventional heating of the substrates with neat ethyl polyphosphate (PPE) for 2 h at 120 °C.[9] 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 seven membered cyclic amidines.[10]

Reactions performed under microwave irradiation proceed in general faster, more cleanly, and with higher yields than with conventional heating.[11] Cyclocondensation is one of the most important methods for the synthesis of heterocycles, and microwave heating has found interesting applications in this area.[12] In previous work, we investigated the use of microwave irradiation to enhance the PPE-promoted synthesis of cyclic amidines.[13]

N-Acyl-*N*′-arylpentamethylenediamines are the synthetic precursors of 1,2-disubstituted hexahydrodiazocines and other acyclic cadaverine derivatives. All these compounds are of biochemical and pharmacological interest as natural polyamine analogs.[14–16] The reported synthetic method for *N*-benzoyl-*N*′-aryl pentamethylenediamines involves the reaction of *N*-acylpiperidines with PCl_5 followed by aminolysis.[17] The overall yields are moderate, and the procedure is restricted to *N*-acyl derivatives without α-hydrogens.[18] In the context of our research,[19] functionalization of *N*-arylcadaverines **3** seemed an interesting alternative for the preparation of selectively *N,N*′-disubstituted 1,5-diamines and related heterocyclic amidines.

Results and discussion

N-acyl-*N*′-arylpentamethylenediamines **2** were synthesized by the sequence shown in Scheme 1.

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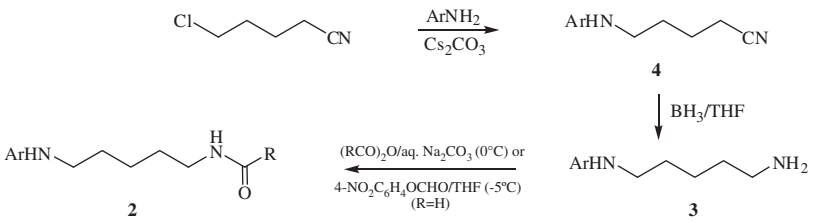
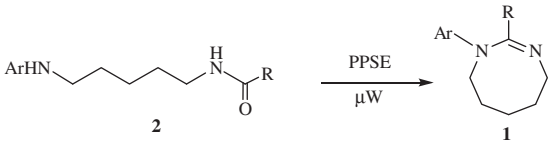


Scheme 1. Synthesis of *N*-acyl-*N*′-arylcadaverines **2**.



Scheme 2. Synthesis of compounds **1**.

Table 1
Synthesis of *N*-acyl-*N*′-aryl-1,5-pentanediamines **2**

Compound **2**	Ar	R	Yield[a] (%)
a	4-$CH_3C_6H_4$	C_2H_5	75
b	4-$CH_3C_6H_4$	*iso*-C_3H_7	95
c	4-$CH_3C_6H_4$	C_6H_5	Quant.
d	4-ClC_6H_4	H	80
e	4-ClC_6H_4	CH_3	87
f	4-ClC_6H_4	C_2H_5	Quant.
g	4-ClC_6H_4	*iso*-C_3H_7	95
h	4-ClC_6H_4	*tert*-C_4H_9	90
i	4-ClC_6H_4	C_6H_5	Quant.
j	4-BrC_6H_4	CH_3	78
k	4-BrC_6H_4	C_2H_5	76
l	4-BrC_6H_4	*iso*-C_3H_7	85
m	C_6H_5	H	70
n	C_6H_5	*iso*-C_3H_7	Quant.

[a] Yields correspond to pure compounds.

Precursors **3** were prepared using the method previously developed by our group.[20] Aminoamides **2a–c,e–l,n** were synthesized by selective acylation of diamines **3** with carboxylic acid anhydrides,[19g] while the reaction of diamines **3d,m** with 4-nitrophenyl formate led selectively to *N*-aryl-*N*′-formyl-1,5-pentanediamines **2d,m** (Table 1).

Cyclodehydration reactions leading to eight membered cyclic amidines require prolonged reaction times and harsh conditions under conventional heating. As already mentioned, reaction conditions described in the literature for 1,2-diaryl derivatives involve heating the substrate for 2 h in neat PPE.[9] In a previous report, we showed that the microwave irradiation of *N*-aryl-*N*′-benzoylpentamethylenediamines with a chloroform solution of PPE under reflux drastically reduces the reaction times and leads to high yields of 1,2-diarylhexahydro-1,3-diazocines.[13a] In connection to this, we recently reported the cyclodehydration of *N*-aryl-*N*′-acyl-1,4-butanediamines with a chloroformic solution of PPE as an efficient method for the preparation of 1-aryl-2-alkyl-1*H*-1,4,5,6-tetrahydrodiazepines.[19g] In such conditions, however, considerably lower yields of a homologous hexahydrodiazocine were obtained.

Previous results of our group indicated that PPSE is capable of efficiently promoting cyclodehydration of certain substrates, which could not be achieved with PPE.[10b,d] PPSE is a mild aprotic dehydrating agent which has been employed in various synthetically useful organic transformations, including heterocycles syntheses.[21] This prompted us to investigate the use of PPSE for the synthesis of 1-aryl-2-alkyl-1,4,5,6,7,8-hexahydro-1,3-diazocines **1**.

Table 2
Synthesis of compounds **1** via Scheme 2

Compound **1**	Ar	R	Yield[a] (%)
a	4-$CH_3C_6H_4$	C_2H_5	58
b	4-$CH_3C_6H_4$	*iso*-C_3H_7	60
e	4-ClC_6H_4	CH_3	50
f	4-ClC_6H_4	C_2H_5	61
g	4-ClC_6H_4	*iso*-C_3H_7	84
j	4-BrC_6H_4	CH_3	52
k	4-BrC_6H_4	C_2H_5	61
l	4-BrC_6H_4	*iso*-C_3H_7	81
m	C_6H_5	H	27[b]

[a] Yields correspond to pure compounds.
[b] The reported yield is approximate and was estimated by integration of suitable ^{1}H NMR signals (see Supplementary data).

Reaction of compound **2a** with PPSE in dichloromethane under microwave irradiation at reflux (15 min at 70 °C) led to the corresponding cyclic amidine **1a** in 42% yield. Working in solvent-free conditions in an open vessel, the reaction was completed in 40 min. at 90 °C. In such conditions, aminoamides **2a,b,e–g,j–m** were converted into the corresponding hexahydrodiazocines **1**. Isolated yields are shown in Table 2.

The expected reactivity of the amide moiety present in precursors **2** follows the order R = H > methyl > ethyl > *iso*-propyl. Conversely, amidines with sterically hindering C2 substituents are less reactive toward hydrolysis. Analysis of the results shows that, in general, yields increase along with the steric hindrance of the R substituent (Table 2). We might therefore conclude that stability of the reaction products is the main factor that conditions the experimental yields. This is in line with our previous results on 1,2-diarylhexahydro-1,3-diazocines,[13a] which are further stabilized by the π-conjugating 2-aryl substituent.[22] In fact, such compounds were obtained in high yields employing a less reactive dehydrating agent, and in milder reaction conditions (PPE/chloroform).[13a]

Conclusions

In conclusion, we have developed a novel method to hitherto unreported 1-aryl-2-alkyl-1,4,5,6,7,8-hexahydro-1,3-diazocines **1**, by microwave-assisted cyclodehydration of *N*-acyl-*N*′-aryl-1,5-pentanediamines **2** with PPSE in solvent-free conditions. The proposed synthetic route allows for the preparation of derivatives with primary and secondary 2-alkyl substituents, not accessible through previously reported methods. Moreover, this is one of the few examples of ring closure reactions leading to eight membered heterocyclic systems described in the literature.

The precursor aminoamides **2** were synthesized by the functionalization of *N*-arylcadaverines **3**. Such acyclic and heterocyclic *N*-arylcadaverine derivatives are potentially bioactive compounds as synthetic polyamine analogs, and some of them represent useful precursors of selectively *N,N*′-disubstituted 1,5-pentanediamines.[23]

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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.2011.09.097.

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