A practical synthesis of N-alkyl-N-arylputrescines and cadaverines

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Abstract

We present an efficient method for the synthesis of *N*-aryl-*N*-alkyl tetra and pentamethylenediamines **1** (putrescines and cadaverines, respectively), by K_2CO_3/KI-mediated *N*-alkylation of *N*-alkylanilines with ω–chloronitriles followed by reduction. The first step was optimized achieving complete selectivity toward the desired *N*-monoalkylation products **2**, which were reduced without purification. The whole sequence involves two steps and one column purification, and leads to high yields of the diamines.

Keywords

N-alkylation; alkylenediamines; cadaverine; polyamines; putrescine

Introduction

Selectively *N*-substituted 1,4-diaminobutane (putrescine) and 1,5-diaminopentane (cadaverine) derivatives are of biochemical and pharmacological interest as synthetic analogs of natural polyamines [1]. Several derivatives have been described acting as antibiotics, antineoplastics, antiparasitic agents, and NMDA or cholinergic modulators [2]. In addition, such compounds represent key intermediates for acyclic and heterocyclic polyamine derivatives [3].

The methods usually employed for the synthesis of symmetrically *N,N´*-disubstituted 1,*n*-diamines involve functionalization of the parent diamine and are not applicable to unsymmetrical derivatives, which require more elaborated strategies [4]. In particular, selectively *N*-substituted putrescines and cadaverines represent a challenge, since the available methods for di and trimethylenediamines are not generally suitable for their higher homologs. Several syntheses of *N*-alkyl (or aralky) tetra and pentamethylenediamines have already been described [5], but only a few general methods are available for *N*-aryl derivatives. The literature regarding *N*-alkyl-*N*-arylputrescines and cadaverines **1** is even scarcer.

In previous work we presented some preliminary results on the synthesis of diamines **3** by Cs_2CO_3 mediated *N*-alkylation of anilines with ω–chlorobutyro (or valero)nitrile followed by reduction [6]. An alternative synthesis was afterwards reported, by aminolysis of *N*-(ω–chloroalkyl)amides followed by deprotection [7a]. The limiting step of the sequence was the synthesis of the precursors [7b], and the overall yields of the method were modest. More recently, Ramírez *et al.* reported a three-step strategy starting from ω–haloalkanoyl chlorides [7c], in which the substituted amino group is generated from an amide, while the primary amine results from reduction of an azide [8].

N-Alkylation is conceptually the most straightforward disconnection towards secondary and tertiary amines [9]. Although at first sight this transformation seems rather simple, the fact that the newly formed amines are also nucleophilic brings about bis and/or polyalkylation byproducts. Thus, the crude reaction mixture often

contains the desired product together with the starting amine and variable amounts of collateral products, all of them with similar R_f values, which complicates the chromatographic purification of the desired compounds. Therefore, improvement in the selectivity of the reaction would not only have a positive impact on the chemical yields but also lead to easier purification protocols.

In this context, new methodologies combining operational simplicity, high yields, readily available starting materials and low cost reagents are desirable for the high throughput preparation of the target compounds.

In this work we present a practical method for the synthesis of tertiary *N*-aryltetra and pentamethylenediamines **1**, by selective monoalkylation of *N*-alkylanilines followed by reduction. The optimized reaction conditions resulted in a simplified procedure, remarkable selectivity in the alkylation step and high global yields of the diamines.

Experimental

***N*-alkyl-*N*-aryl-1,*n*-diamines (1) (n=4,5). General procedure.**

A solution of the corresponding halonitrile (2.5 mmol) in DMF (0.5 mL) was added during 1.5 h to a mixture of the arylamine (5 mmol), K_2CO_3 (2.5 mmol) and KI (5 mmol) in DMF (3 mL). The mixture was stirred at 100ºC for 5 hs. After completion of the reaction, as indicated by TLC, the mixture was treated with ethyl ether (50 mL) and water (10 mL). The aqueous phase was separated and extracted with ethyl ether (30 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated *in vacuo*.

The resulting crude product was treated with saturated borane/THF. The solution was refluxed for 2 hs, cooled and treated with methanol. The solvent was then eliminated *in vacuo*. The residue was refluxed with 10% hydrochloric acid (30 mL), filtered and made alkaline with 10% aqueous sodium hydroxide. The alkaline mixture was extracted with ethyl acetate (4x20 ml). The organic phase was washed with water (5 ml), dried over sodium sulphate and filtered. The solvent was

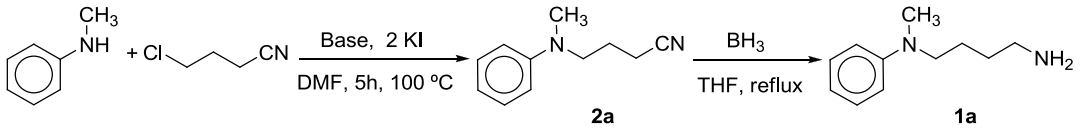
eliminated *in vacuo*. The crude product was purified by column chromatography (Silica gel, dichloromethane: isopropylamine).

Results and Discussion

N-Alkyl-*N*-arylputrescines and cadaverines

In view of the potential interest of the compounds, and in order to widen the scope of our method [6], we turned our attention to the synthesis of *N*-aryl-*N*-alkylputrescines and cadaverines **1**. To our knowledge, only a few examples of such compounds were already reported in the literature [7c, 10].

We examined in the first place the synthesis of *N*-methyl-*N*-phenylputrescine **1a** (Scheme 1) using different reaction conditions for the *N*-alkylation step, as shown in Table 1.



Scheme 1.

Table 1: Optimization of the reaction conditions.

Entry	Base	Molar ratio[a]	Yield (% **2a**)[b]	Yield (% **1a**)[b]	Overall yield[b]
1	Cs_2CO_3	1:1	60	81	49
2	K_2CO_3	1:1	74	81	60
3	K_2CO_3	1:1	-	-	78
4	K_2CO_3	2:1	-	-	83
5	Cs_2CO_3	2:1	-	-	60
6[c]	K_2CO_3	2:1	-	-	68

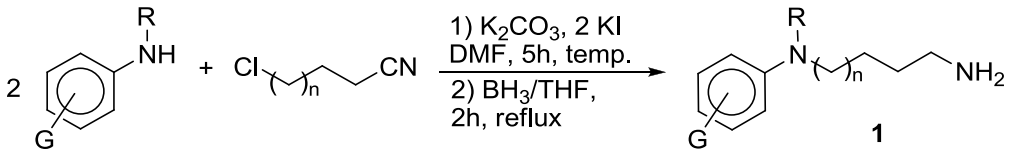
[a] *N*-methylaniline:4-chlorobutyronitrile; [b] Yields correspond to pure compounds; [c] A 4:1 mixture of DME:DMF was used as the solvent.

The starting conditions were chosen on the basis of our preliminary results: equimolar amounts of the reagents, DMF as the solvent, Cs_2CO_3 as the base and KI (2 equiv.) [6]. In such conditions, the *N*-alkylation product (**2a**) was obtained with 60% yield. Reduction of aminonitrile **2a** with BH_3/THF (81%) led to *N*-methyl-*N*-

phenylputrescine **1a** (49% overall yield) (Table 1, entry 1). A significant improvement in the yield was observed employing K_2CO_3 as the base in the first step (Table 1, entry 2). Furthermore, TLC analysis of the crude aminolysis product showed the absence of bisalkylation product, allowing for its reduction without previous purification. This led to a further increase in the overall yield (Table 1, entry 3), and simplified considerably the whole procedure. In fact, the small R*f* difference between *N*-methylaniline and compound **2a** complicates its chromatographic purification. In contrast, the crude reduction product contained only the arylamine and compound **1a** (ΔR*f* >0.6, dichloromethane), and was easily purified by short-column filtration. As expected for a S_N2 reaction, on changing the molar ratio arylamine: halonitrile from 1:1 to 2:1, a further improvement in the yield was observed (Table 1, entry 4).

In a control experiment, the reaction run with Cs_2CO_3 as the base, a twofold excess of the arylamine and without purification of the aminolysis product gave significantly lower yields (Table 1, entry 5). The same effect was observed when a 4:1 mixture of DME: DMF was used as the solvent (Table 1, entry 6).

Employing the optimized experimental conditions (Scheme 2), a series of *N*-aryl-*N*-alkyl cadaverines and putrescines **1b-i** were prepared in high global yields, as shown in Table 2.



Scheme 2: Synthesis of *N*-alkyl-*N*-arylputrescines and cadaverines **1**.

Table 2: Synthesis of *N*-alkyl-*N*-arylputrescines and cadaverines **1b-i**.

Compd. **1**	R	n	G	Temp. (°C)	Yield (% **1**)[a]
b	C_2H_5	1	H	100	75
c	*iso*-C_3H_7	1	H	100	71
d	C_2H_5	1	4-Cl	110	64
e	C_2H_5	1	4-CH_3	100	73
f	C_2H_5	1	2-CH_3	110	70
g	CH_3	2	H	100	87
h	C_2H_5	2	H	100	83
i	*iso*-C_3H_7	2	H	100	77
j	C_2H_5	2	4-Cl	110	69
k	C_2H_5	2	4-CH_3	100	75
l	C_2H_5	2	2-CH_3	110	71

[a] Yields correspond to pure compounds.

Analysis of the results evidences some general trends. As expected, substrates with less steric hindrance in the R moiety (**1a-c** and **1g-i**) showed comparatively higher yields. At variance with our previous results [6], the sequence led to better results when 5-chlorovaleronitrile was used as the alkylating agent. Regarding the arylamines, compounds bearing an electron withdrawing group (**1d,j**) and *ortho* substituted derivatives (**1f,i**) required higher temperatures in the first step and showed slightly lower yields.

Conclusion

In conclusion, we have developed an efficient protocol for the high throughput synthesis of tertiary *N*-arylputrescines and cadaverines. Such compounds are potentially bioactive as synthetic analogs of the natural polyamines. The sequence employs readily available and inexpensive starting materials, and involves two steps and one column purification. It represents an advantageous alternative to

other synthetic approaches [7a, c] regarding yields, number of steps and operational simplicity.

Aknowledgments

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