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

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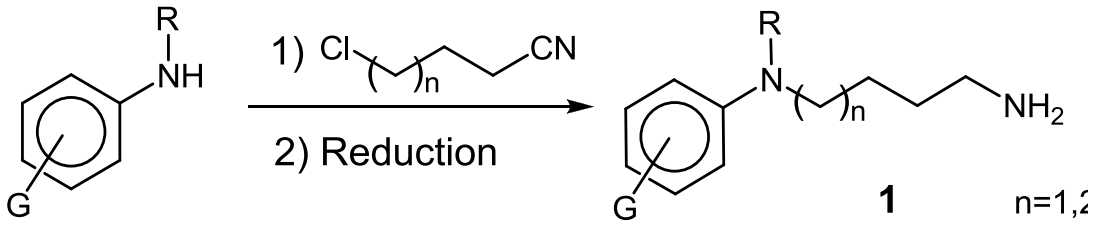
# Introduction

Selectively *N*-substituted 1,4-diaminobutane (putrescine) and 1,5-diaminopentane (cadaverine) derivatives:

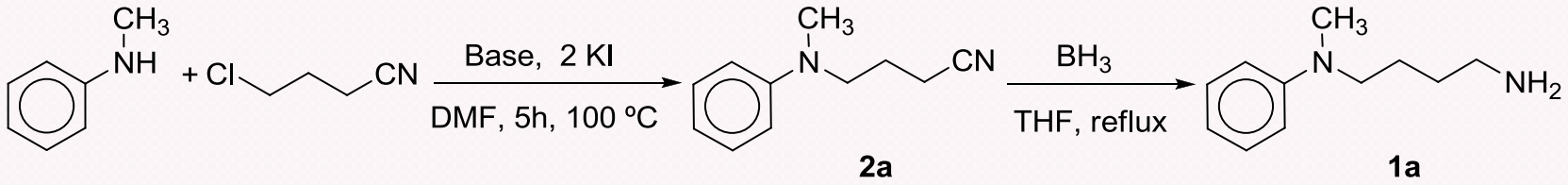
- Synthetic analogs of natural polyamines
- Antibiotics
- Antineoplastics
- Antiparasitic agents
- NMDA or cholinergic modulators.

**Proposed synthetic approach**



# Results and discussion

Optimization of the reaction conditions



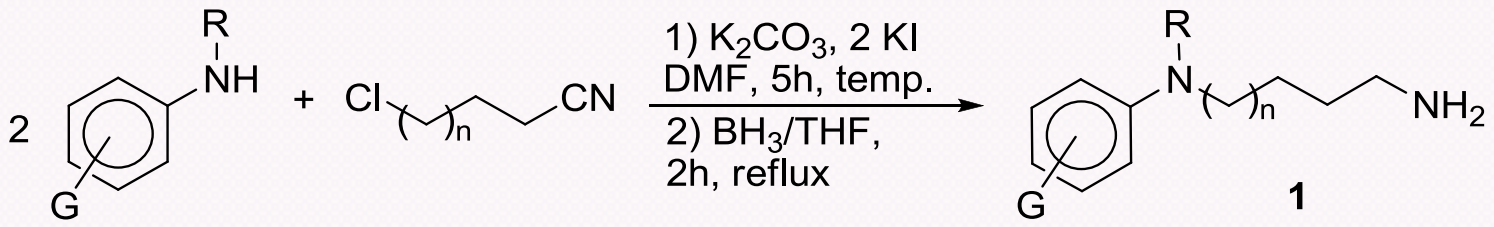

| Entry | Base | Molar ratio[a] | Yield (% 2a)[b] | Yield (% 1a)[b] | Overall yield[b] |
|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | 1:1 | 60 | 81 | 49 |
| 2 | $K_2CO_3$ | 1:1 | 74 | 81 | 60 |
| 3 | $K_2CO_3$ | 1:1 | - | - | 78 |
| 4 | $K_2CO_3$ | 2:1 | - | - | 83 |
| 5 | $Cs_2CO_3$ | 2:1 | - | - |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

**BEST CONDITIONS**:

- Solvent= DMF
- Base= $K_2CO_3$
- Molar ratio= 2:1

# Synthesis of *N*-alkyl-*N*-arylputrescines and cadaverines **1**




| Compd. 1 | R | n | G | Temp. (°C) | Yield (% 1) |
|---|---|---|---|---|---|
| **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 |

❖ Substrates with less steric hindrance in the R moiety (**1a-c** and **1g-i**) showed comparatively higher yields.

❖ The sequence led to better results when 5-chlorovaleronitrile was used as the alkylating agent

❖ 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.

# CONCLUSIONS

- We have developed an efficient protocol for the high throughput synthesis of tertiary *N*-arylputrescines and cadaverines
- 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 regarding yields, number of steps and operational simplicity.