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

María Cruz Mollo, Liliana R. Orelli
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**

![Proposed synthetic approach diagram]
Results and discussion

Optimization of the reaction conditions

| Entry | Base     | Molar ratio | Yield (% 2a) | Yield (% 1a) | Overall yield |
|-------|----------|-------------|--------------|--------------|---------------|
| 1     | Cs₂CO₃   | 1:1         | 60           | 81           | 49            |
| 2     | K₂CO₃   | 1:1         | 74           | 81           | 60            |
| 3     | K₂CO₃   | 1:1         | -            | -            | 78            |
| 4     | K₂CO₃   | 2:1         | -            | -            | 83            |
| 5     | Cs₂CO₃   | 2:1         | -            | -            | 60            |
| 6⁶    | K₂CO₃   | 2:1         | -            | -            | 68            |

**BEST CONDITIONS:**
- Solvent= DMF
- Base= K₂CO₃
- Molar ratio= 2:1

\[ N\text{-}methylaniline:4\text{-}chlorobutyronitrile; \]
\[ \text{Yields correspond to pure compounds;} \]
\[ A 4:1 \text{ mixture of DME:DMF was used as the solvent.} \]
Synthesis of $N$-alkyl-$N$-arylpentrescines and cadaverines 1

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.

| Compd.  | R     | n | G            | Temp. (°C) | Yield (%) |
|---------|-------|---|--------------|------------|-----------|
| b       | C$_2$H$_5$ | 1 | H            | 100        | 75        |
| c       | iso-C$_3$H$_7$ | 1 | H            | 100        | 71        |
| d       | C$_2$H$_5$ | 1 | 4-Cl         | 110        | 64        |
| e       | C$_2$H$_5$ | 1 | 4-CH$_3$     | 100        | 73        |
| f       | C$_2$H$_5$ | 1 | 2-CH$_3$     | 110        | 70        |
| g       | CH$_3$   | 2 | H            | 100        | 87        |
| h       | C$_2$H$_5$ | 2 | H            | 100        | 83        |
| i       | iso-C$_3$H$_7$ | 2 | H            | 100        | 77        |
| j       | C$_2$H$_5$ | 2 | 4-Cl         | 110        | 69        |
| k       | C$_2$H$_5$ | 2 | 4-CH$_3$     | 100        | 75        |
| l       | C$_2$H$_5$ | 2 | 2-CH$_3$     | 110        | 71        |
CONCLUSIONS

- We have developed an efficient protocol for the high throughput synthesis of tertiary $N$-arylpolyamines 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.