N-Cyclopropylation of Aromatic Amines

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Various aromatic amines have been *N*-cyclopropylated in excellent overall yields in a two-step sequence of 1-ethoxycyclopropylation followed by reduction.

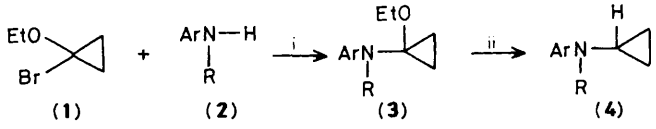
Cyclopropylamines are a well known class of compounds, some of which are physiologically active, for example as irreversible inhibitors of monoamine oxidase and cytochrome P-450.[1] However, the simple incorporation of a cyclopropyl group into a heteroatomic terminus, *e.g.* an amino group, of a molecule is difficult to achieve because cyclopropyl halides are extremely resistant to nucleophilic attack.[2] We now report a simple indirect method, which utilizes a temporary activating group on the cyclopropane ring.

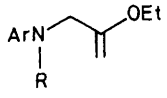
An excess (1.2—2 equiv.) of readily available 1-bromo-1-ethoxycyclopropane (**1**)[3] was stirred with various aromatic amines (**2**) in the presence of triethylamine as an acid scavenger in a *non-polar* refluxing solvent such as dichloromethane or pentane (2—3 M).[4] *N*-(1-Ethoxycyclopropyl)-arylamines (**3**) were exclusively obtained (Table 1; 67—94%); no trace of the ring-opened enol ethers (**5**) was found.[2] Compounds (**3**) could be reduced with a variety of reducing agents in the presence of a Lewis acid. A mixture of $NaBH_4$

Table 1. Preparation of aryl *N*-cyclopropylamines.[a]

Amine (2)	1-Ethoxycyclopropylation[b] Reaction time/h[c]	Yield of (3)/%	Reductive de-ethoxylation[e] Time/h (temp./°C)	Yield of (4)/%
a	29	83	1 (0)	96
b	36	85	1 (reflux)	74
c	24	80	12 (reflux)	45
d	12	80	1 (0)	87
e	24	90	1 (reflux)	84
f	26	94	1 (23)	100
g	48	64[d]	1 (reflux)	82
h	24	86	4 (23)	81
i	25	84	2 (23)	100
j	17	67	1 (0)	100

[a] All compounds gave spectral data in agreement with the proposed structures. [b] ArNHR, (**1**) (2 equiv.), and Et_3N (2 equiv.) in refluxing solvent (substrate concentration 3 M). [c] All in CH_2Cl_2 except (**2i**) in pentane. [d] Accompanied by recovery of starting material (**2g**), 21%. [e] The ethoxy compounds (**3**) were stirred with a precombined mixture of $NaBH_4$ (2 equiv.) and $BF_3{\cdot}OEt_2$ (2 equiv.) in THF (substrate concentration 0.5 M).





a; Ar = Ph, R = H
b; Ar = 1-naphthyl, R = H
c; Ar = 2-naphthyl, R = H
d; Ar = 3-MeC_6H_4, R = H
e; Ar = 2-ClC_6H_4, R = H
f; Ar = 3-BrC_6H_4, R = H
g; Ar = 4-$NO_2C_6H_4$, R = H
h; Ar = 4-$EtO_2CC_6H_4$, R = H
i; Ar = 3-Cl, 4-FC_6H_3, R = H
j; Ar = Ph, R = Me

Scheme 1. *Reagents and conditions:* i, (**1**) (1.2—2 equiv.), dichloromethane or pentane (2—3 M solution), reflux; ii, $NaBH_4$ (2 equiv.), $BF_4{\cdot}OEt_2$ (2 equiv.), THF (stirred at 0 °C for 0.5 h before use).

(2 equiv.) and $BF_3{\cdot}OEt_2$ (2 equiv.) in tetrahydrofuran (THF), which had been stirred at 0 °C for 0.5 h, was very effective for the reductive de-ethoxylation, giving satisfactory yields of the corresponding *N*-cyclopropylamines (**4**) (Table 1). The secondary amine (**2j**) could also be cyclopropylated in good overall yields, but aliphatic amines such as dodecyl- and cyclohexyl-amines did not react.

The simple *N*-cyclopropylation of aromatic amines reported herein should provide ready access to new cyclopropylamines by structural modification of existing compounds.

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