Practical Synthesis of *N*-Cyclopropylanilines via Direct Condensation of Anilines with [(1-Ethoxycyclopropyl)oxy]trimethylsilane

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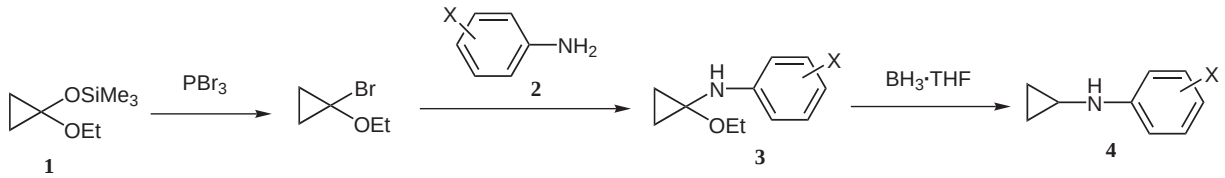
Abstract: *N*-Cyclopropylanilines were obtained in high yield through the condensation reaction of anilines with [(1-ethoxycyclopropyl)oxy]trimethylsilane by a simple two-steps operating process, without purification of the intermediate, 1-alkoxy-1-anilinocyclopropane.

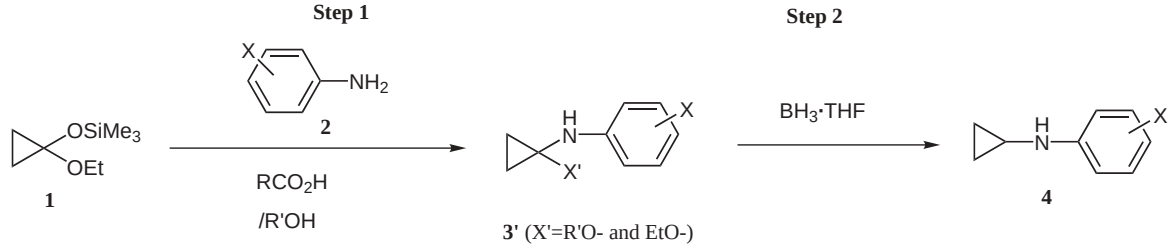
Key words: *N*-cyclopropylanilines, condensation reaction, reductive dealkoxylation, borane, cyclopropanone

N-Cyclopropylanilines, which especially contain fluorine substituents, are important intermediates for the preparation of quinolinecarboxylic acids useful as synthetic antimicrobial agents, such as ciprofloxacin or sparfloxacin.[1] However the simple incorporation of cyclopropyl group into aryl amino group is difficult because cyclopropyl halides are extremely resistant to nucleophilic attack. So preparation of these compounds was reported to be performed by *N*-cyclopropylation of anilines using [(1-ethoxycyclopropyl)oxy]trimethylsilane,[2] which is equivalent to cyclopropanone as ketal form. This procedure consists of: 1) bromination of [(1-ethoxycyclopropyl)oxy]trimethylsilane, 2) substitution reaction with anilines and 3) reductive dealkoxylation with BH_3·THF complex (Scheme 1).[3] However, this method is rather tedious as it is necessary to substitute the ethoxy group in **1** with bromine, a better leaving group. However, such 'activated cyclopropane', 1-bromo-1-ethoxycyclopropane, would have been thermally unstable and needed to be treated carefully, so application of this method for large-scale preparation was difficult.[4]

Now we wish to report a new procedure, which can avoid the use of unstable 1-bromo-1-ethoxycyclopropane and is also suitable for the industrial production of *N*-cyclopropyl-aniline derivatives. Thus we found that [(1-ethoxycyclopropyl)oxy]trimethylsilane (**1**) easily condensed with aniline derivatives **2** in the presence of an organic acid such as AcOH or formic acid in alcoholic solvents (**Step 1**),[5] to give the intermediate, 1-alkoxy-1-anilinocyclopropane. The crude products of **Step 1**, obtained as the mixture **3′**, consist mainly of 1-alkoxy-1-anilinocyclopropanes and small amount of 1-ethoxy-1-anilinocyclopropanes **3** (see Table 1). After removal of the solvent and the organic acids in vacuo, **3′** was readily dealkoxylated to give *N*-cyclopropylanilines **4** by reducing agents (**Step 2**) in good yield (Scheme 2).[6]



Scheme 1



Scheme 2

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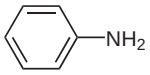
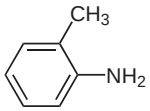
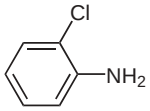
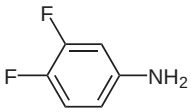
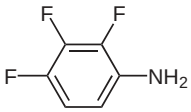
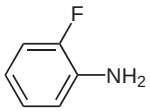
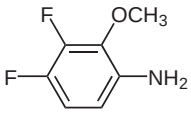
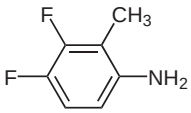
Table 1 Preparation of *N*-Cyclopropyl Anilines

Entry[a]	**Step1**					**Step 2**					
	Starting materials	AcOH[b]	**1**[b]	Time[c] (h)	**3′**(%)[d] (MeO/ EtO)	Lewis Acid[b]	$NaBH_4$[b]	Temp (°C)	Time (h)	Prod-ucts	Yield of **4** (%)[e]
1	 **2a**	3	1.2	5	97 (98:2)	BF_3·THF (1.5)	1.5	60	4	**4a**	75
2	 **2b**	3	1.2	7	97 (97:3)	BF_3·THF (1.5)	1.5	60	3	**4b**	86
3	 **2c**	3	1.2	9	97 (98:2)	BF_3·THF (1.5)	1.5	60	7	**4c**	92
4	 **2d**	3	1.2	1.5	97 (96:4)	BF_3·Et_2O (1.5)	1.5	r.t.	4	**4d**	67
5	 **2e**	3	1.2	13	88 (97:3)	BF_3·THF (1.5)	1.5	60	8	**4e**	86
6	 **2f**	3	1.2	6.5	86 (98:2)	BF_3·THF (1.5)	1.5	60	17	**4f**	82
7	 **2g**	4	1.2	3	93 (97:3)	BF_3·Et_2O (2)	2.0	r.t. 66	5 2	**4g**	89
8	**2g**	4	1.2	6	97 (97:3)	BF_3·THF (1.2)	1.2	r.t. 60	2.5 9	**4g**	89
9	**2g**	4	1.2	4	96 (96:4)	$AlCl_3$ (0.5)	1.5	5 r.t.	3 3	**4g**	72
10	 **2h**	4	1.3	4	–[f]	BF_3·Et_2O (1.2)	1.2	r.t. 50	3 3	**4h**	85

[a] Entries 1–7 and 9 were performed using 50 mmol (in entries 8 and 10, 0.2 mol) of anilines (**2a**–**h**), and 1 L/mol of MeOH (**Step 1**). In entries 1–9, 1.5 L/mol (in entry 10, 1.2 L/mol) of THF (**Step 2**) was used as the solvent.
[b] Values show the molar ratios to anilines (**2a**–**h**).
[c] Carried out under reflux (67–69 °C).
[d] Determined by GC analysis of the reaction mixture.
[e] Isolated yield.
[f] Not reported in detail.

Before we began our study, Gillaspy et al. had reported the one-pot *N*-cyclopropylations of amines using large excess of **1** (4.0–6.0 equiv more than amines) followed by the reduction by sodium cyanoborohydride. But this method produced biscyclopropylamines in higher amounts than monocyclopropylamines.[7]

In our reaction condition, most of the ethoxy group of [(1-ethoxycyclopropyl)oxy]trimethylsilane (**1**) was substituted by the alkoxy group derived from alcohol used as the solvent, to give the mixture **3′** which was isolated as crude oil by removal of the solvent and the organic acid in vacuo. The nature of alkoxy group such as methoxy, ethoxy, isopropoxy, did not cause significant effect on the yields of the final product **4**.[11] The reductive dealkoxylation of **3′** was effectively performed by BH_3·THF complex prepared from BF_3·THF (or BF_3·Et_2O) and $NaBH_4$. In most of our experiments, excess of Lewis acids and $NaBH_4$ were used (theoretical molar ratio of BF_3 and $NaBH_4$ to **2** is 0.5 and 0.375 respectively when **3′** is formed quantitatively). But we could reduce these values.[8] The reduction using $NaBH_4/AlCl_3$ also gives the desired *N*-cyclopropylanilines **4**. The reduction by BH_3·THF complex gave better yield and less by-products than that by $NaBH_4/AlCl_3$.[9] These results are summarized in Table 1.[10]

These reactions somewhat depend on the substituents of aromatic ring. The *ortho*-substituted anilines gave better yields and fewer by-products. However in the case of no substituents at the *ortho* position, the yield was relatively low (entries 1 vs 2–4 and entry 4 vs 5, 8). We considered that stability of the intermediate, 1-alkoxy-1-anilinocyclopropane (**3′**), during solvent evaporation in acidic media is increased by existence of the *ortho*-substituents, such as, chloro, fluoro, methyl or methoxy group. But the condensation reaction of *ortho*-substituted anilines proceeds relatively slow compared to those with substituents at other positions. Especially, 2-nitroaniline reacted extremely slowly because of the strong electron-withdrawing group.[12]

In summary, we have found a very convenient method for the synthesis of *N*-cyclopropylaniline derivatives; the intermediates of quinolinecarboxylic acids useful as synthetic antimicrobial agents and this method is applicable for the laboratory scale to the industrial preparation scale. This method should find utility in medicinal and synthetic organic chemistry.

References

(1) (a) Michael, S.; Uwe, P.; Klaus, G.; Andreas, K. EP 0332033 A2, **1989**. (b) Mcguirk, P. R.; Conn, L. US Pat 5039682 A, **1991**.

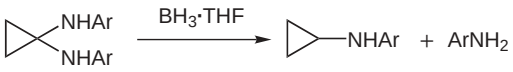
(2) (a) Rühlmann, K. *Synthesis* **1971**, 236. (b) Salaün, J.; Marguerite, J. *Org. Synth.* **1985**, *63*, 147.

(3) Kang, J.; Kim, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 897.

(4) Miller, S. A.; Gadwood, R. C. *Org. Synth.* **1989**, *67*, 210.

(5) Employing AcOH and formic acid seemed to give the same results, but we used AcOH due to better handling and lower toxicity.

(6) The crude **3′** also contains 2–3% of 1,1-dianilinocyclopropane as a by-product, which is readily dealkoxylated to give **4** and equimolar amount of aniline (see Scheme 3).



Scheme 3

(7) Gillaspy, M. L.; Lefker, B. A.; Hada, W. A.; Hoover, D. J. *Tetrahedron Lett.* **1995**, *36*, 7399.

(8) For example, the molar ratio of BF_3·THF and $NaBH_4$ to **2g** could be reduced to 1.05 each without decreasing the yield of **4g**.

(9) When $NaBH_4/AlCl_3$ was used in **Step 2**, the reaction proceeded smoothly, but 14% of *N*,*N*-dicyclopropyl-3,4-difluoro-2-methoxyaniline was found in the product (entry 9). The reason why such large amount of this by-product was formed is not clear (normally <1%). But intermolecular migration of cyclopropyl group seemed have occurred in this reagent system.

(10) Typical reaction procedure (entry 7) is as follows: Into a 200 mL four-necked flask fitted with a reflux condenser, a magnetic stirrer and a thermometer were fed 3,4-difluoro-2-methoxyaniline (**2g**, 7.96 g, 50 mmol), AcOH (12.0 g, 200 mL) and MeOH (50 mL). After [(1-ethoxycyclopropyl)oxy]-trimethylsilane (**1**, 10.0 g, 57.4 mmol) was added dropwise at r.t., the reaction mixture was refluxed at 67–69 °C for 3 h under N_2 atmosphere. Then the mixture was concentrated in vacuo using a rotary evaporator, to obtain crude oil **3g′** (11.52 g) which contained 90.1% of *N*-(1′-methoxy)cyclopropyl-3,4-dimethoxyaniline and 2.7% of *N*-(1′-ethoxy)cyclopropyl-3,4-dimethoxyaniline, analyzed by GC and GC–MS.
Into a 200 mL four-necked flask fitted with a reflux condenser, a mechanical stirrer and a thermometer were fed $NaBH_4$ (3.78 g, 100 mmol) and anhyd THF (50 mL). After cooling to 5 °C and adding BF_3·Et_2O complex (14.19 g, 100 mmol) dropwise, the mixture was stirred under N_2 atmosphere for 1 h at 5 °C. Then, crude **3g′** dissolved in THF (25 mL) was added dropwise at 5–10 °C in a time period of 20 min. After stirring at r.t. for 5 h, at reflux temperature for 2 h, and recovering THF (60 mL) by distillation, the mixture was cooled to r.t. and poured into water (300 mL). Then the resulting mixture was extracted with Et_2O (2 × 100 mL). The Et_2O layer was washed with water (2 × 100 mL) and dried over anhyd Na_2SO_4 followed by the removal of Et_2O by a rotary evaporator, to obtain a crude oil (10.56 g). The oil was subjected to distillation under reduced pressure to give *N*-cyclopropyl-3,4-difluoro-2-methoxy-aniline (**4g**) (8.83g, 89%); bp 71–73 °C/0.53 kPa.

(11) The effect of alcohol used in **Step1** was studied in the following manner: 3,4-Difluoro-2-methoxyaniline(**2g**) was employed to react in both EtOH and *i*-PrOH. The molar ratio of reagents and volume of alcohol (L/mol) was identical with that in entry 7. After refluxing in EtOH for 5 h, 87.1% of *N*-(1′-ethoxy) cyclopropyl-3,4-dimethoxyaniline was formed (determined by GC). Employing the conditions described in **Step 2** (**2g**:$NaBH_4$:BF_3·THF = 1:1.2:1.2) at r.t. for 1 h and at 60 °C for 6 h, *N*-cyclopropyl-3,4-difluoro-2-methoxy-aniline (**4g**) was isolated in 83% yield. On the other hand, **Step 1** in *i*-PrOH required higher temperature and substitution of the ethoxy group in **3′** by *i*-PrOH proceeded rather sluggishly. Thus after reaction at 70 °C for 4 h and refluxing (87 °C) for 4 h, 62.8% of *N*-(1′-isopropoxy)-cyclopropyl-3,4-dimethoxyaniline and 14.5% of *N*-(1′-

ethoxy) cyclopropyl-3,4-dimethoxyaniline were formed (isopropoxy/ethoxy = 81:19, determined by GC). On the contrary, most of the ethoxy groups in **3′** were replaced by methoxy group when MeOH was used (see Table 1). After following **Step 2** (at r.t. for 1 h and 60 °C for 6 h at the same reagent ratio as in EtOH), 70% of **4g** was isolated. Thus in **Step 1** the compositions of crude **3g′** obtained by these reactions were somewhat different from that in MeOH, but this did not give a large effect on **Step 2**. The lower yield of **4g** in EtOH and *i*-PrOH than that in MeOH arises from the production of relatively large amount (ca 5–10%) of 1,1-bis(3,4-difluoro-2-methoxyanilino) cyclopropane as the by-product (see ref. 6). From these points it can be gathered that employing MeOH as solvent in **Step 1** gave the best yield of **4**.

(12) When 2-nitroaniline (50 mmol), [(1-ethoxycyclopropyl)-oxy] trimethylsilane(**1**) (57.5 mmol), AcOH (200 mmol), and MeOH (50 mL) were mixed and refluxed for 15 h, 7.3% of *N*-(1′-methoxy)cyclopropyl-2-nitroaniline was produced (determined by GC and GC–MS).