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Boron trifluoride-mediated synthesis of *N*-aryl-substituted pyrrolidines from tetrahydrofuran and amines

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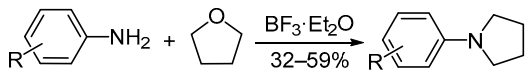


R = H, F, Cl, NO_2, Me

Boron trifluoride-mediated transformation of tetrahydrofuran to corresponding *N*-aryl-substituted pyrrolidines is conducted under mild reaction conditions, providing a practical synthetic method with reasonable yields. Computational studies confirmed the reaction mechanism involving a fast Lewis acid-assisted ring-opening step, followed by the 7-membered intermediate formation and a ring-closing process as the rate-determining step.

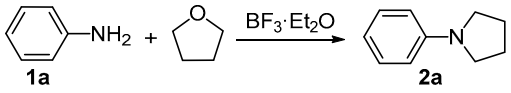
Keywords: *N*-aryl-substituted pyrrolidines, cyclic ether, Lewis acid, tetrahydrofuran activation, ring opening.

N-substituted azacycles are important structural motifs of organic molecules, as well as useful building blocks, and a substantial amount of work has been done on their synthesis. Commonly used methods of their synthesis include reactions of dihalides or diols with primary amines,[1–5] reactions of halides with *N*-unsubstituted azacycles,[6–10] hydrogenantion of the corresponding amides.[11] Pyrrolidine derivatives can also be obtained from nitrogen-containing acetals and ketals.[12] Synthesis of *N*-substituted azacycles from primary amines and cyclic ethers is valuable due to the formation of water as the only waste product, as well as wide availability of starting materials.[13–16] The main limitation of this method is the requirement of drastic reaction temperature[13,14] in traditional cases, nevertheless new mediators and catalysts have been exploited to facilitate the reaction. For example, the employment of dimethylaluminum amide reagents[17] and the approach *via* $B(C_6F_5)_3$-mediated frustrated Lewis pair pathway.[18]

As a part of our ongoing studies on C–N bond formation reactions,[19,20] we found that the appropriate Lewis acid such as titanium tetrachloride can promote the ring opening of cyclic ethers, incorporate primary amine and cyclic ether in a metallacyclic intermediate, and facilitate the C–N bond formation to provide *N*-substituted azacycles.[21] Computational investigations suggested that in the case of the aluminum amide-mediated reaction similar process may occur, but with different rate-determining step.[17] To gain further understanding of the similarities and differences between the congener reactions and provide new choices for the synthesis of *N*-substituted azacycles, as well as to expand the reaction to other effective and easier handled Lewis acids we continued our research. Herein we report a boron trifluoride-mediated transformation of THF to the corresponding *N*-aryl-substituted pyrrolidines.

In our previous studies on the related transformation of arylamines and cyclic ethers into *N*-substituted azacycles, some commonly used Lewis acids such as $AlCl_3$, $FeCl_3$, and $ZnCl_2$ were shown to be unable to promote the reaction. However, it was encouraging to find out in a subsequent test that boron trifluoride etherate facilitates the reaction. Further optimization of the reaction conditions was carried out using aniline (**1a**) and THF in the model reaction. We found out that slight excess of THF was necessary for reasonable yields (Table 1, entries 1–3), but large excess of THF decreases boiling temperature of the reaction mixture and reduces product yield (entry 4). Increasing reaction temperature effectively benefited the process (entry 5 *vs.* entry 3), while extension of the reaction time improved the yields slightly (entry 6 *vs*. entry 5). The reactant ratio was originally set as **1a**:THF:$BF_3 \cdot Et_2O$ = 1:10:1.2 according to the existing study on the titanium-mediated reaction.[21] It turned out that decreasing the amount of $BF_3 \cdot Et_2O$ (entry 7 *vs*. entry 5) markedly impaired the yield, while increasing the amount of $BF_3 \cdot Et_2O$ was not a beneficial factor either (entry 8 *vs*. entry 5). Thus, the reaction conditions were finally set as refluxing in xylenes for 24 h with a ratio of 1:10:1.2 between the reactants.

Table 1. Optimization of reaction conditions between aniline (**1a**) and THF*



1a **2a**

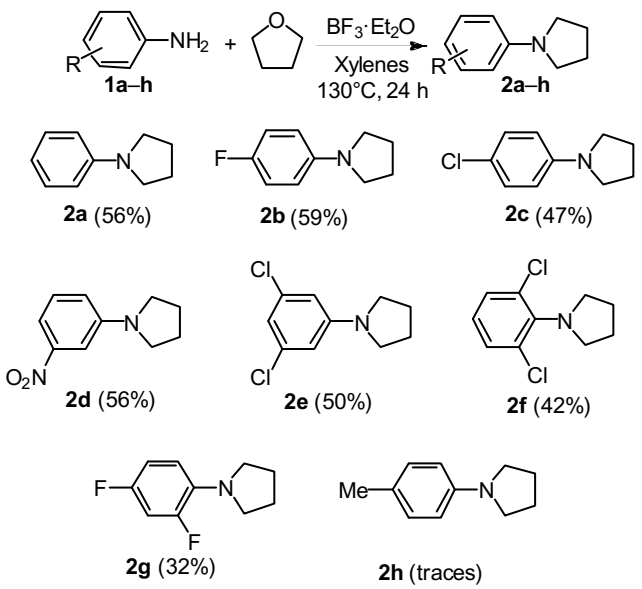
Entry	**1a**: THF :BF_3·OEt_2	Solvent	Temperature, °C	Time, h	Isolated yield, %
1	1:1:1.2	Toluene	110	24	<5
2	1:3:1.2	Toluene	110	24	19
3	1:10:1.2	Toluene	110	24	28
4	1:20:1.2	Toluene	110	24	26
5	**1:10:1.2**	**Xylenes**	**130**	**24**	**56**
6	1:10:1.2	Xylenes	130	36	59
7	1:10:1.0	Xylenes	130	24	26
8	1:10:2.0	Xylenes	130	24	42

* All reactions were carried out on a 1 mmol scale.

The scope of the reaction was then examined using the optimized reaction conditions, giving products **2a–h** in moderate yields (Scheme 1). Generally speaking, amines with electron-withdrawing substituents on the benzene ring (compounds **2b**,**c**,**e**) are suitable substrates and active functional groups, like nitro group (compound **2d**), are also tolerable. Substitution at the *ortho* position of the benzene ring is undesirable due to the steric hindrance (compounds **2f**,**g**). Thus, no product was isolated when substrate with large group like *o*-trifluoromethyl was employed despite the favorable effect from the strong electron-withdrawing properties of the group. To our regret, amines with electron-donating substituents on the benzene ring, such as *p*-methylaniline (compound **2h**), do not work as effectively as those with electron-withdrawing substituents, yielding low amount of products.

Our previous studies suggest that Lewis acids with a different metal center could assist the reaction discussed here in a similar way, but with a different rate-determining step.[21] We wondered whether a similar mechanism could also reasonably explain the reactivity of a nonmetallic Lewis acid, like boron trifluoride etherate, and what, in application to this case, the rate-determining step would be. Thus, the calculational study of the current reaction was carried out referring to the computational studies on the titanium-mediated reaction.[21] The results indicated that in a way similar to the titanium- and aluminum-mediated reactions, the BF_3·Et_2O-mediated conversion here involves a seven-membered ring intermediate II (Fig. 1). Like in the $AlMe_3$ case, boron-mediated reaction involves the ring-

Scheme 1



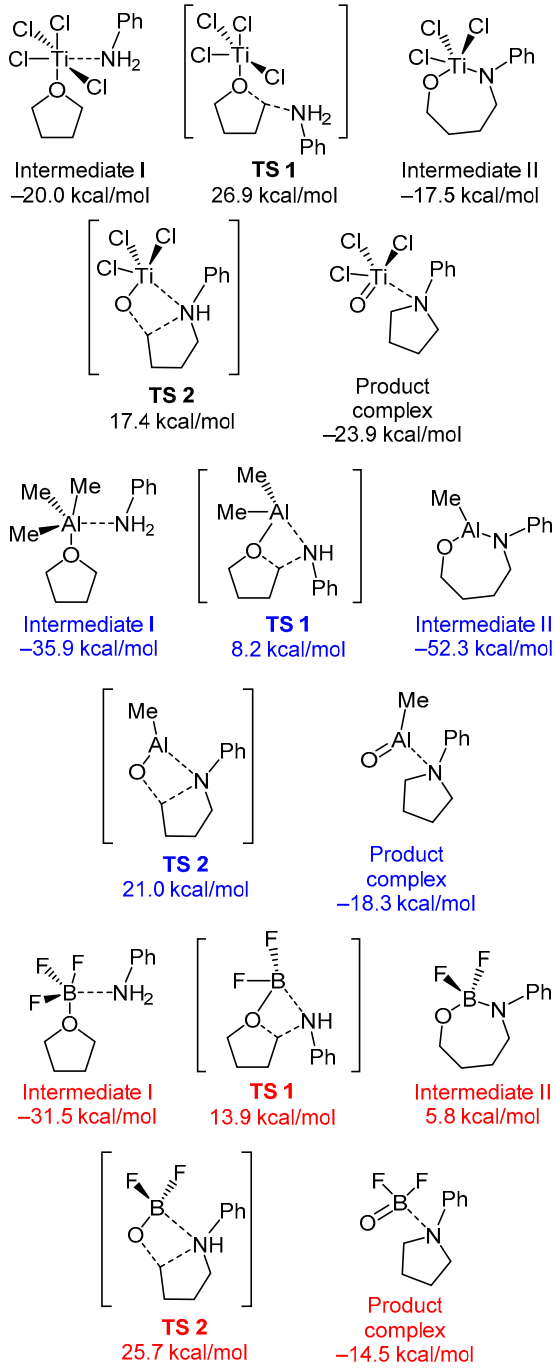


Figure 1. Geometries and energies for the key structures in the $TiCl_4$-mediated (black), $AlMe_3$-mediated (blue), and BF_3·Et_2O-mediated (red) conversion of THF to pyrrolidine **2a**.

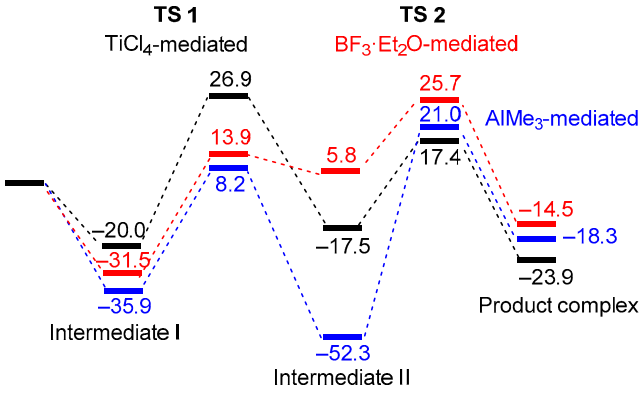


Figure 2. Energy profiles for $TiCl_4$-mediated (black), $AlMe_3$-mediated (blue), and $BF_3·Et_2O$-mediated (red) conversion of THF to pyrrolidine. Gibbs free energies are given in kcal/mol.

closing process **TS 2** as rate-determining step, while the ring-opening **TS 1** is the rate-determining step in the titanium-mediated reaction. The energy profile following the existing mechanism gave a reasonable activation energy requirement of 25.7 kcal/mol, which was compatible with the experimental outcomes (Fig. 2). The activation energy was clearly larger than that in the $AlMe_3$ case (21.0 kcal/mol) and comparable to the titanium-mediated reaction (26.9 kcal/mol).

In summary, boron trifluoride etherate was proved to be a practical mediator in the transformation of arylamines and tetrahydrofuran to the corresponding *N*-arylpyrrolidines under mild reaction conditions. Calculational study suggested a reasonable activation energy which was compatible with experimental results in a mechanism involving a Lewis acid-assisted ring opening of the cyclic ether and a boron-facilitated rate-determining ring-closing process.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AV400 NMR spectrometer (400 and 100 MHz, respectively) with $CDCl_3$ as solvent and TMS as internal standard at room temperature. All reactions were carried out under N_2 atmosphere in a Schlenk flask.

THF was distilled from sodium and benzophenone. All other reagents were purchased from TCI Co., Ltd. and J&K Co., Ltd.

Synthesis of *N*-arylpyrrolidines 2a–g (General method). A solution of $BF_3·Et_2O$ (0.15 ml, 1.2 mmol) and arylamine (1 mmol) in dry xylenes (4 ml) was stirred at room temperature for 30 min. THF (1.0 ml, 10 mmol) was added to the mixture and the temperature slowly elevated to 130°C. Mixture was refluxed for 24 h, then cooled to room temperature. Saturated $NaHCO_3$ solution (10 ml) and dichloromethane (10 ml) were added and stirring continued for 1 h. Then mixture was extracted with CH_2Cl_2 (3×10 ml), combined CH_2Cl_2 extracts dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent CH_2Cl_2–hexane, 1:4) to give *N*-arylpyrrolidines **2a**–**g**. Physical properties of the compounds are in good correlation with the literature data.[17,21,22]

1-Phenylpyrrolidine (2a).[17,21] Yield 82 mg (56%), pale-yellow liquid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.28–7.16 (2H, m, H-3,5 Ph); 6.66 (1H, t, *J* = 7.9, H-4 Ph); 6.57 (2H, d, *J* = 7.9, H-2,6 Ph); 3.28 (4H, t, *J* = 6.5, $N(CH_2)_2$); 2.04–1.93 (4H, m, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm: 148.1 (C-1 Ph); 129.2 (C-3,5 Ph); 115.4 (C-4 Ph); 111.7 (C-2,6 Ph); 47.6 ($N(CH_2)_2$); 25.5 ($N(CH_2\underline{C}H_2)_2$).

1-(4-Fluorophenyl)pyrrolidine (2b).[17,21,22] Yield 97 mg (59%), yellow liquid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.99–6.90 (2H, m, H-3,5 Ar); 6.52–6.45 (2H, m, H-2,6 Ar); 3.25 (4H, t, *J* = 6.6, $N(CH_2)_2$); 2.04–1.99 (4H, m, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 154.8 (d, $^1J_{CF}$ = 232.9, C-4 Ar); 144.8 (C-1 Ar); 115.5 (d, $^2J_{CF}$ = 22.2, C-3,5 Ar); 112.1 (d, $^3J_{CF}$ = 7.4, C-2,6 Ar); 48.1 ($N(CH_2)_2$); 25.5 ($N(CH_2\underline{C}H_2)_2$).

1-(4-Chlorophenyl)pyrrolidine (2c).[21,22] Yield 85 mg (47%), white solid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.14 (2H, d, *J* = 8.6, H-3,5 Ar); 6.45 (2H, d, *J* = 8.6, H-2,6 Ar); 3.24 (4H, t, *J* = 6.0, $N(CH_2)_2$); 2.00 (4H, t, *J* = 6.0, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm: 146.5 (C-4 Ar); 128.9 (C-1 Ar); 120.1 (C-3,5 Ar); 112.6 (C-2,6 Ar); 47.7 ($N(CH_2)_2$); 25.5 ($N(CH_2\underline{C}H_2)_2$).

1-(3-Nitrophenyl)pyrrolidine (2d).[21] Yield 108 mg (56%), orange solid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.45 (1H, d, *J* = 7.5, H-4 Ar); 7.31 (2H, m, H-2,5 Ar); 6.81 (1H, d, *J* = 6.8, H-6 Ar); 3.34 (4H, t, *J* = 5.7, $N(CH_2)_2$); 2.06–2.08 (4H, m, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm: 149.3 (C-3 Ar); 148.2 (C-4 Ar); 129.5(C-1 Ar); 117.2 (C-2 Ar); 109.8 (C-5 Ar); 105.6 (C-6 Ar); 47.8 ($N(CH_2)_2$); 25.5 ($N(CH_2\underline{C}H_2)_2$).

1-(3,5-Dichlorophenyl)pyrrolidine (2e).[21] Yield 108 mg (50%), pale-yellow liquid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.94 (1H, s, H-4 Ar); 6.48 (2H, s, H-2,6 Ar); 3.23 (4H, t, *J* = 5.6, $N(CH_2)_2$); 2.02–1.98 (4H, m, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 149.0 (C-3,5 Ar); 135.2 (C-1 Ar); 114.9 (C-4 Ar); 109.8 (C-2,6 Ar); 47.6 ($N(CH_2)_2$); 25.4 ($N(CH_2\underline{C}H_2)_2$).

1-(2,6-Dichlorophenyl)pyrrolidine (2f).[21] Yield 91 mg (42%), white solid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.31 (2H, d, *J* = 7.3, H-3,5 Ar); 7.01 (1H, t, *J* = 7.0, H-4 Ar); 3.36–3.33 (4H, m, $N(CH_2)_2$); 2.04–2.01 (4H, m, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm: 143.3 (C-2,6 Ar); 136.6 (C-1 Ar); 128.9 (C-3,5 Ar); 126.0 (C-4 Ar); 49.8 ($N(CH_2)_2$); 26.5 ($2N(CH_2\underline{C}H_2)_2$).

1-(2,4-Difluorophenyl)pyrrolidine (2g).[17,21] Yield 58 mg (32%), yellow liquid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.70–6.80 (2H, m, H-5,6 Ar); 6.61 (1H, td, *J* = 9.3, *J* = 2.3, H-3 Ar); 3.31 (4H, td, *J* = 6.4, *J* = 2.2, $N(CH_2)_2$); 2.01–1.89 (4H, m, $N(CH_2C\underline{H}_2)_2$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 154.8 (dd, J_{CF} = 237.9, J_{CF} = 11.0, C-4 Ar); 151.9 (dd, J_{CF} = 245.3, J_{CF} = 11.2, C-2 Ar); 134.4 (d, J_{CF} = 12.2, C-5 Ar); 115.2 (dd, J_{CF} = 8.7, J_{CF} = 6.2, C-6 Ar); 104.5 (t, J_{CF} = 25.5, C-3 Ar); 110.0 (dd, J_{CF} = 21.3, J_{CF} = 3.3, C-1 Ar); 50.0 (d, J_{CF} = 4.5, $N(CH_2)_2$); 25.0 ($N(CH_2\underline{C}H_2)_2$).

Computational calculations. Full geometrical optimizations were carried out using the Gaussian 09[23] suite of programs, employing the Minnesota density functional M06. The 6-31+G** basis set was used on nonmetallic atoms while the SDD basis set was employed on Ti. The

solvent effect was calculated using conductor-like polarizable continuum model in toluene. Frequency calculations were performed at the same level to identify all of the stationary points as minima (zero imaginary frequency) or transition states (one imaginary frequency) and intrinsic reaction coordinates were calculated for each transition state to confirm that the structure indeed connects the two relevant minima.

The Supplementary information file containing computational data of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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