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Efficient One-Pot Synthesis of Fluorinated Benzimidazolines, Benzothiazolines, Benzoxazolines, and Dihydrobenzoxazinones Using Gallium(III) Triflate as a Catalyst

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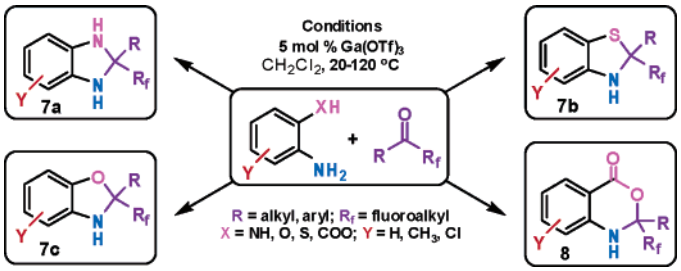
ABSTRACT



One-pot synthesis of fluorinated benzimidazolines, benzothiazolines, benzoxazolines, and dihydrobenzoxazinones was easily achieved under mild conditions in high yields and purity through gallium(III) triflate mediated condensation–cyclization. Introduction of fluorine atoms favors the formation of the five-membered heterocycles over seven-membered heterocycles.

Lewis acid catalysis in organic synthesis has been well documented in the literature.[1] The majority of the strong and efficient Lewis acids such as $AlCl_3$, $AlBr_3$, SbF_5, etc. used in various organic transformations are prone to fast hydrolysis and deactivate readily. Quite often, they are required in stoichiometric amounts, are not reusable, and lead to secondary reactions, making the reaction workup and product isolation tedious. It has been found that gallium(III) trifluoromethanesulfonate [$Ga(OTf)_3$, gallium triflate] acts as an effective but mild and nonhydrolyzable Lewis acid catalyst for many organic synthetic transformations, such as Friedel−Crafts alkylation, acylation and hydroxyalkylation, dehydration of oximes to the corresponding nitriles, Beckman rearrangement, epoxyolefin cyclization, annulation, etc.[2] The catalyst is stable (up to 280 °C) and used in low amounts (∼5 mol %), easily recovered from the aqueous reaction mixture, and reusable, showing its significant potential as a safer and environmentally benign catalyst.[3] It can be easily

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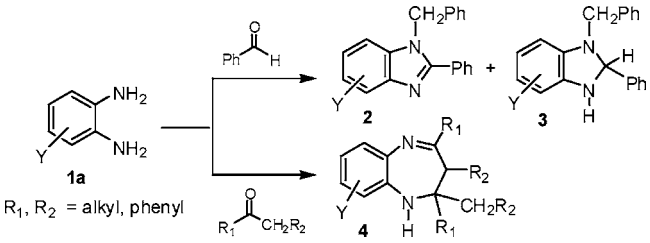
synthesized by reacting $GaCl_3$ or metallic gallium with trifluoromethanesulfonic acid.[4] Herein, we report our results for the efficient one-pot synthesis of fluorinated benzimidazolines **7a**, benzothiazolines **7b**, benzoxazolines **7c**, and dihydrobenzoxazinones **8** using gallium(III) triflate as a catalyst by reaction with *o*-aminoarene derivatives.

Benzimidazolines, benzothiazolines, benzoxazolines, and dihydrobenzoxazinones are important classes of heteroaromatics. Benzimidazolines, often called organic hydrides, can act as good reducing agents and good hydrogen storage materials in many organic reactions.[5,6] Benzothiazolines and benzoxazolines are used as plant growth regulants, herbicides, and anticonvulsants, in photochromic dyes, and for the treatment of ADD (attention defficiency disorder).[7] Dihydrobenzoxazinones are used in analgesics and also as useful building blocks for drugs and pharmaceuticals, which possess antiviral, antifungal, antibacterial, and antiparasitic properties.[8] We were interested in synthesizing the fluorinated analogues of these classes of compounds, as it is well-known that presence of fluorine can result in substantial changes in the biological properties of organic compounds.[9] Incorporation of fluorine in drug molecules can highly affect their physicochemical properties, such as bond strength, liophilicity, bioavailability, conformation, electrostatic potential, dipole moment, pK_a, etc.; pharmacokinetic properties, such as tissue distribution; rate of metabolism; or pharmacological consequences, such as pharmacodynamics and toxicology.

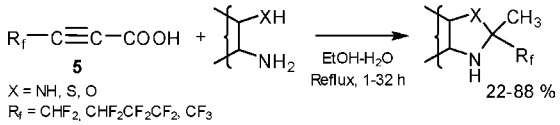
Benzimidazolines **3** are generally synthesized from the reaction of 1,2-phenylenediamines **1a** and benzaldehyde (Scheme 1).[10] However, when ketones (R_1, R_2 = alkyl, phenyl) were used under similar conditions, 1,5-benzodiazepine derivatives **4** were formed as the major products (Scheme 1).[11] This reaction proceeds through the diimine intermediate **10a**, which then undergo an internal Michael-type addition reaction to give rise to the corresponding 1,5-benzodiazepine derivatives **4** (Scheme 4).

Scheme 1. Reactions of Benzaldehyde and Ketones with 1,2-Phenylenediamines



Reports on the direct synthesis of fluorinated benzimidazolines are very rare.[12] To the best of our knowledge, an easy and convenient method is not yet known. Funabiki et al.[13] have prepared fluorinated benzimidazolines from fluorinated butynoic acids **5** (Scheme 2). Synthesis of more diverse and functionalized starting materials for this reaction is tedious. Furthermore, the reaction conditions are harsh, and chemical yields are not so significant. On the other hand, direct syntheses of fluorinated benzimidazolines from fluorinated ketones and diamines have not yet been reported.

Scheme 2. Synthesis of Fluorinated Heterocycles from Fluorinated Butynoic Acids



Therefore, we explored the synthesis of fluorinated benzimidazolines directly from fluorinated ketones and diamines using gallium triflate as the Lewis acid catalyst (Scheme 3). We found that 1,1,1-trifluoroacetone undergoes smooth condensation−cyclization reaction with 1,2-phenylenediamine using 5 mol % of gallium triflate in CH_2Cl_2 at 50 °C (Table 1, entry 1). Many of these reactions are feasible even at room temperature with longer reaction time. The reaction is very clean, and removal of solvent afforded the corresponding trifluoromethylated benzimidazoline derivative **7a** in high yield and purity.

The reaction is also feasible with other common solvents such as THF, CH_3CN, dioxane, etc., but the yield and purity

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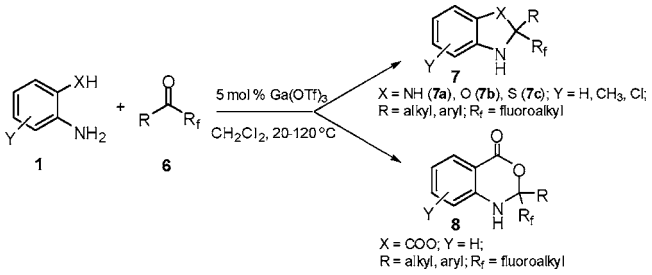
Scheme 3. Synthesis of Fluorinated Heterocyles



of the products are lower. It is noteworthy to mention that unlike in the case of nonfluorinated ketones, no 1,5-benzodiazepine derivative **4** was obtained under these conditions. Intrigued by this fact, we explored this reaction using various diamine derivatives and different fluorinated ketones. Aliphatic, aromatic, and benzylic trifluoromethylated ketones gave clean products with different diamines. Results are shown in Tables 1 and 2. 1,1-Difluoroacetone also gave the corresponding benzimidazoline in good yield and purity (Table 1, entry 7). However, in the case of fluoroacetone, a mixture of benzimidazoline **7** and 1,5-benzodiazepine derivatives **4** was formed. We performed the reaction at lower temperature (0−5 °C) and observed a significant amount of benzimidazoline formation, but the conversion and isolated yield of the product dropped significantly.

As the number of fluorine atoms attached to the α-carbon increases, the electrophilicity at the carbon center of the monoimine intermediate **9** increases. Consequently, the nonbonding electron pair on the nitrogen atom of the second amino group rapidly attacks the highly electrophilic carbon center of the internal fluorinated imine followed by a 1,3-proton transfer, which leads to the formation of the corresponding 5-membered ring (Scheme 4). On the other hand, when no fluorine atom or a single fluorine atom is present in the ketone, the electrophilicity of the monoimine **9a** is not sufficient to undergo internal attack by the electron pair of the nitrogen atom of the second amine group. Thus, the second amine moiety reacts intermolecularly with another molecule of ketone to form the diimine intermediate **10a**, which undergoes further rearrangement and internal Michael-type addition to give rise to the corresponding 7-membered ring (Scheme 4).

We expanded our methodology to synthesize fluorinated thiazolines **7b**, oxazolines **7c**, and oxazinones **8** using the corresponding *o*-amino derivatives. Similar to 1,2-phenylenediamine, the corresponding 2-aminothiophenol, when reacted with 1,1,1-trifluoroacetone, also gave clean benzothiazoline derivative under gallium triflate catalyzed conditions (Table **3**, entry 1). However, the reaction of 1,1,1-trifluoroacetone

Table 1. Preparation of 2-Fluoroalkyl Benzimidazolines

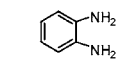
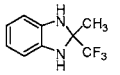
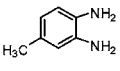
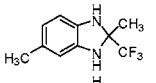
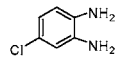
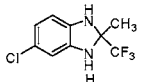
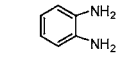
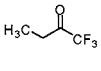
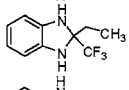
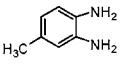
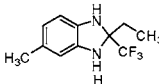
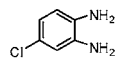
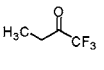
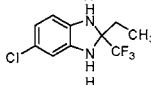
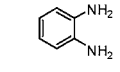
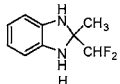
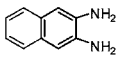
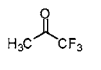
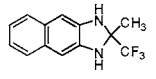
entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yield (%)
1			4	50		97
2			4	50		86
3			4	50		80
4			5	50		83
5			5	50		89
6			5	50		80
7			4	20		85
8			2	120		95

Table 2. Preparation of Trifluromethyl Benzimidazolines

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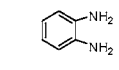
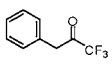
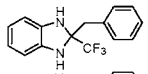
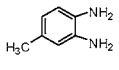
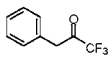
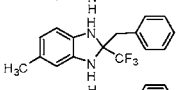
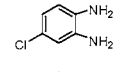
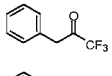
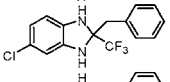
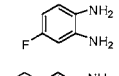
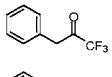
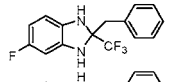
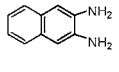
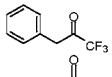
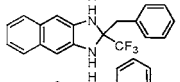
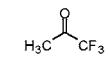
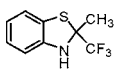
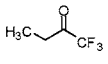
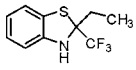
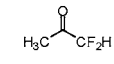
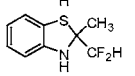
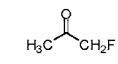
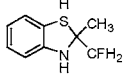
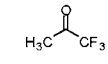
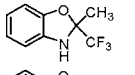
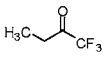
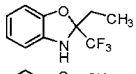
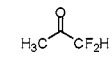
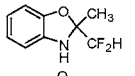
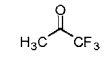
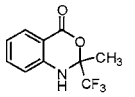
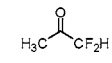
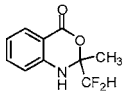
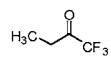
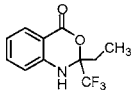
1			2	100		90
2			2	100		87
3			2	100		88
4			2	100		84
5			1	120		85
6			4	120		89
7			3	120		80
8			3	120		92
9			4	120		89

Scheme 4. Mechanism

Table 3. Preparation of Fluorinated Benzothiazolines, Benzoxazolines, and Dihydrobenzoxazinones

entry	amine	fluorinated ketone	time (h)	temp (°C)	product	yield (%)
1			4	50		91
2			4	50		88
3			4	20		98
4			4	20		80
5			4	75		75
6			4	75		60
7			4	20		84
8			7	100		87
9			6	75		63
10			7	100		60

with 2-aminophenol and anthranilic acid require harsher conditions (Table 3, entries 5 and 8). 1,1-Difluoroacetone also gave clean products with all of these *o*-amino derivatives (Table 3, entries 3, 7, and 9). Similar to the case of 1,2-phenylenediamine, a mixture of products was formed when monofluoroacetone was reacted with 2-aminophenol and anthranilic acid, respectively.

However, unlike 1,2-phenylenediamine reaction, in these cases, the amount of the desired monofluorinated product in the mixture was significant. The reaction of monofluoroacetone and 2-aminothiophenol afforded the corresponding monofluorinated benzothiazoline derivative as the major product, which was isolated in 80% chemical yield (Table 3, entry 4). In this case, the rate of the benzothiazoline formation from the monoimine intermediate **9** in intramolecular fashion appeared to be much faster than the intermolecular attack of the second ketone molecule to the monoimine intermediate. Surprisingly, aromatic and benzylic trifluoroketones showed low reactivity toward these *o*-amino derivatives and yields were not significant in most of these cases.

We have also explored the potential of other metal triflate catalysts toward this condensation-cyclization reaction. We found that most of the metal triflate catalysts bring out this reaction efficiently in CH_2Cl_2, except for lanthanum triflate, which gave a very low yield of the product (Table 4, entry 6). However, gallium triflate was found to be superior giving the maximum yield of 2-trifluromethylbenzimidazoline (Table 4, entry 1).

Table 4. Reaction of 1,2-Phenylenediamine with 1,1,1-Trifluoroacetone Using Various Metal Triflates as Catalysts

entry	catalyst	yield (%)
1	$Ga(OTf)_3$	97
2	$Yb(OTf)_3$	93
3	$Y(OTf)_3$	87
4	$Sc(OTf)_3$	96
5	$Sm(OTf)_3$	88
6	$La(OTf)_3$	32
7	$Cu(OTf)_2$	75

In conclusion, gallium triflate is found to be a stable, water tolerant, recoverable, reusable, environmentally friendly, and efficient Lewis acid. Even when used in catalytic amounts, it provides the optimum acidity required for the synthesis of fluorinated benzimidazolines, benzothiazolines, benzoxazolines, and dihydrobenzoxazinones from fluorinated ketones through efficient condensation−cyclization reactions. These reactions are clean, require mild conditions, are easy to workup, and provide the corresponding products in high yield and purity in most cases.

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Note Added after ASAP Publication. CH_2Cl_2 was erroneously printed as CH_2C_{12} throughout the paper in the version published ASAP December 16, 2006; the corrected version was published ASAP December 19, 2006.

Supporting Information Available: General experimental procedure and spectctroscopic data of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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