Organic LETTERS

Letter

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Erbium Triflate Promoted Multicomponent Synthesis of Highly Substituted Imidazoles

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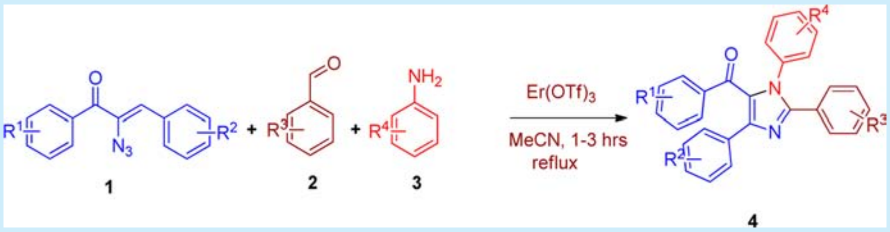
Ⓢ *Supporting Information*

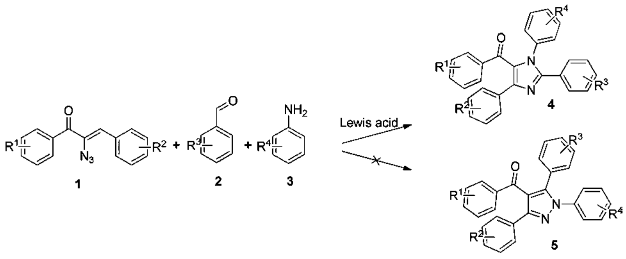


ABSTRACT: The synthesis of highly substituted imidazole derivatives has been achieved from various α-azido chalcones, aryl aldehydes, and anilines. This multicomponent protocol employs erbium triflate as a catalyst resulting in excellent yield of the imidazoles.

Recently, multicomponent reactions have been popularly employed to synthesize biologically active compounds.[1] Libraries of small heterocyclic molecules such as imidazole can be synthesized for possible therapeutic applications.[2] The imidazole ring is a part of histidine and its decarboxylation metabolite, histamine,[3] and the derivatives of imidazole are the core fragments in different natural products.[4] The imidazole derivatives have rich pharmacological applications acting as glucagon receptors,[5] therapeutic agents,[6] antibacterial agents,[7] antitumor agents,[8] and inhibitors of p38 MAP kinase[9] and B-Raf kinase,[10] apart from behaving as plant growth regulators[11] and fungicides.[12] Lewis acid catalyzed multicomponent reactions are effective for various synthetic transformations, and rare earth metal triflate catalyzed organic reactions have gained attention during the past decade.[13,14] Lewis acid promoted reactions assume importance as Lewis acids like lanthanide triflates[15] are mild reagents, recoverable, and reusable and, thus, environmentally friendly with no special affinity toward moisture. Very few typical methodologies exist for the assembly of highly substituted imidazoles. Polysubstituted imidazoles via the oxidative dehydrogenative reactions have been recently reported.[16]

In recent years, much attention has been directed toward α-azido chalcones, which are versatile synthons for the nitrogen-containing heterocycles.[17−20] This paper outlines the utility of α-azido chalcones in preparing highly substituted imidazoles (Scheme 1).

Scheme 1. Planning for the Synthesis of Imidazole

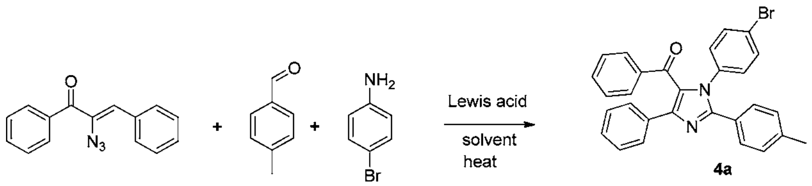


Recently, Lewis acid promoted synthesis of polysubstituted pyrroles from α-azido chalcones and 1,3-dicarbonyl compounds has been described by us.[21] The scope of the α-azido chalcones have been further explored in this work to create a different heterocyclic system, highly substituted imidazoles.

In a typical procedure, a mixture of α-azido chalcone **1** ($R_1 = R_2 = H$), 4-methylbenzaldehyde **2** (R_3 = 4-methyl), and 4-bromoaniline **3** (R_4 = 4-bromo) was stirred well in the appropriate solvent for 10 min along with a small amount of Lewis acid, after which the mixture was heated for a few hours. This resulted in the formation of 1-(4-bromophenyl)-2-(4-methylphenyl)-4-phenyl-5-benzoylimidazole, **4a**, and not even a trace of pyrazole derivative **5** (Scheme 1). Encouraged by this, the conditions were then optimized to obtain a maximum yield of the imidazole derivatives. Different Lewis acids such as BF_3, $AlCl_3$, $FeCl_3$, and $InCl_3$ have been tried, but lanthanum triflates, particularly erbium triflate, seem to be most effective as a catalyst in this reaction. The results are presented in Table 1. The reaction takes place comfortably in acetonitrile as the

Received: November 28, 2013
Published: January 15, 2014

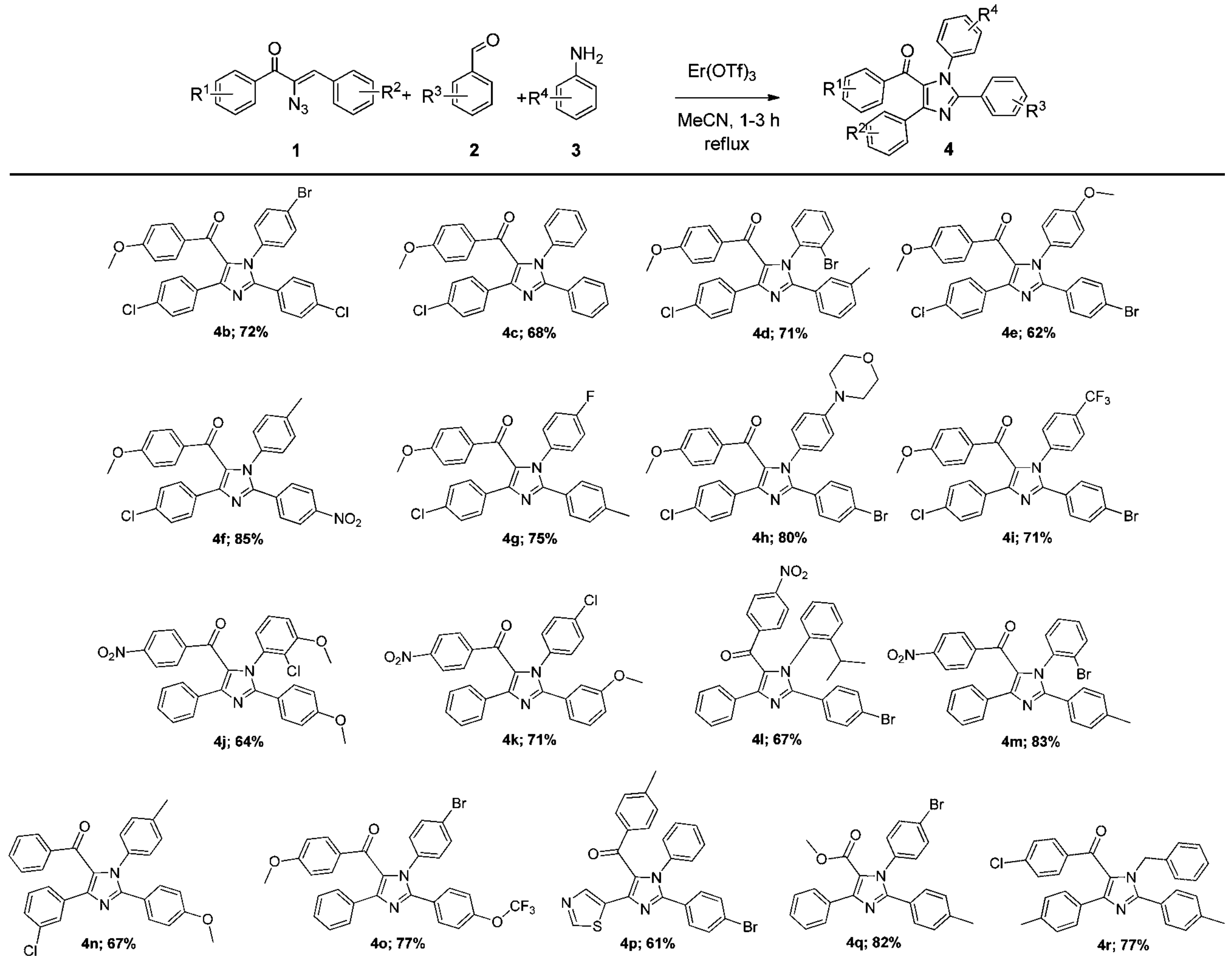
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	equivalent (mmol)	solvent	temp (°C)	time (h)	yield of **4a** (%)
1	BF_3	1	MeCN	70	8	65
2	$AlCl_3$	1	MeCN	70	16	
3	$FeCl_3$	1	MeCN	70	12	
4	$InCl_3$	0.02	MeCN	70	8	35
5	$Er(OTf)_3$	0.02	MeCN	70	2	88
6	$Yb(OTf)_3$	0.02	MeCN	70	3	70
7	Nil	0.02	MeCN	70	8	
8	$Er(OTf)_3$	0.02	1,4-dioxane	80	10	45
9	$Er(OTf)_3$	0.02	THF	80	16	38
10	$Er(OTf)_3$	0.02	DCE	70	8	54
11	$Er(OTf)_3$	0.02	DMF	100	16	14
12[b]	nil	nil	nil	100	0.4	

[a] Reaction Conditions: Refluxing with solvent **1** (0.2 mmol), **2** (0.2 mmol), **3** (0.2 mmol), catalyst (0.004 mmol), solvent (10 mL). [b] Neat reaction carried out under microwave conditions at 100 °C for 15 min.

Scheme 2. One-Pot Synthesis of 4b−r



4b; 72% **4c; 68%** **4d; 71%** **4e; 62%**

4f; 85% **4g; 75%** **4h; 80%** **4i; 71%**

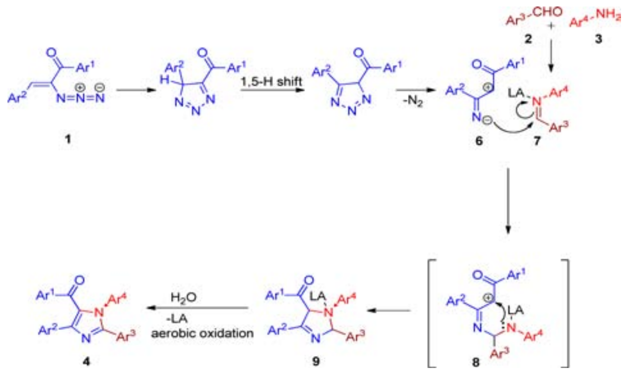
4j; 64% **4k; 71%** **4l; 67%** **4m; 83%**

4n; 67% **4o; 77%** **4p; 61%** **4q; 82%** **4r; 77%**

solvent, while solvents such as DMF, DCE, THF, and dioxane were less efficient. Attempts to carry out the transformation in the absence of a catalyst or in the absence of solvent were not successful. After the conditions were optimized, the reaction was carried out with differently substituted α-azido chalcones, benzaldehyde, and anilines to obtain a library of compounds **4b–r** (Scheme 2). This one-pot synthesis works with α-azido cinnamate, instead of α-azido chalcone, as well (**4q**). The reaction is successful with an aliphatic amine also (**4r**). However, the reaction is not proceeding with aliphatic aldehydes, nitroanilines and 2-substituted benzaldehydes in the expected path under the optimized conditions.

A plausible mechanism for the formation of aryl(1,2,4-triaryl-1*H*-imidazol-5-yl)methanone **4** is shown in Scheme 3.

Scheme 3. Proposed Reaction Mechanism



Initially, Lewis acid coordinated imine **7** could have been generated from substituted benzaldehyde **2** aniline **3** in the presence of Lewis acid. The vinyl azides easily generate the species **6**.[22] The lone pair of electrons on the nitrogen atom of **6** might have attacked the electrophilic center of the imine intermediate forming **8**. Then the electron pair over the imine nitrogen could attack the α-position of the carbonyl-forming dihydro imidazole **9**. Air oxidation of **9** would have led to **4**. The reaction has also been carried out under nitrogen atmosphere, and after workup, it was found that the product obtained is the oxidized product. Probably during the working up, when the crude product is exposed to atmosphere, the air oxidation would have taken place.

All of the α-azido chalcones were synthesized from the corresponding benzylidene acetophenones in two steps following the literature procedure.[23] The structure of **4a** was confirmed by spectral data and single-crystal X-ray analysis of **4a** (Figure 1).[24]

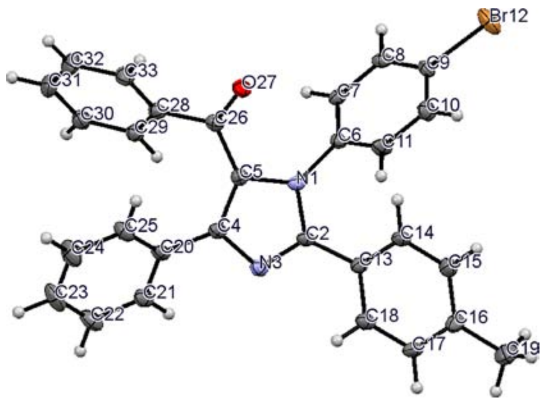


Figure 1. Crystal structure of **4a**.

In conclusion, using readily available starting materials, we have demonstrated a new simple route for the synthesis of pharmaceutically important phenyl(1,2,4-triphenyl-1*H*-imidazol-5-yl)methanone derivatives using an eco-friendly catalyst.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization of new compounds, and crystal data of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank DST, New Delhi, for assistance under the IRHPA program for the NMR facility. Financial support from CSIR, New Delhi, to K.R. is gratefully acknowledged for the award of a Junior Research Fellowship.

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