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1,1′-Carbonyldiimidazole mediates the synthesis of N-substituted imidazole derivatives from Morita–Baylis–Hillman adducts

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ABSTRACT

In this Letter, we describe a simple and straightforward method for the synthesis of N-substituted imidazole derivatives. 1,1-carbonyldiimidazole mediates the process, which requires no activation group step. We obtained imidazole derivatives in high yields and with short reaction times. To demonstrate the synthetic significance of the aforementioned compounds, we also describe the synthesis of novel ionic liquids from these derivatives.

Introduction

Over the years, the imidazole nucleus has attracted the attention of the scientific community due to its chemical and biological properties.[1] For example, this nucleus is present in the structures of several natural products in the form of the essential amino-acid histidine or in alkaloids exhibiting anti-tumoral and anti-bacterial activities.[2] A great numbers of medicines contain the imidazole nucleus, including ketoconazole (**1**), metronidazole (**2**), and cimetidine (**3**), which are used to treat fungal infections, bacterial infections, and gastric ulcers, respectively (Fig. 1).[3]

In addition, compounds containing the imidazole nucleus can be used as ligand, because they can serve as precursors for *N*-heterocyclic carbenes (*N*HC) and/or catalysts for chemical reactions. Imidazole-containing compounds are also used as a platform for the synthesis of various types of ionic liquids.[4]

The Morita–Baylis–Hillman reaction is an organocatalyzed transformation that forms a new σ C–C bond and a new stereogenic center. This reaction allows for easy access to multi-functionalized and versatile small molecules, allowing the development of a rich and diverse chemistry.[5–7]

Morita–Baylis–Hillman adducts have been used as substrates for the preparation of N-substituted imidazole derivatives. One such approach is based on an S_N2 reaction between allyl bromides, prepared from MBH adducts, and imidazole (Scheme 1).[7–9]

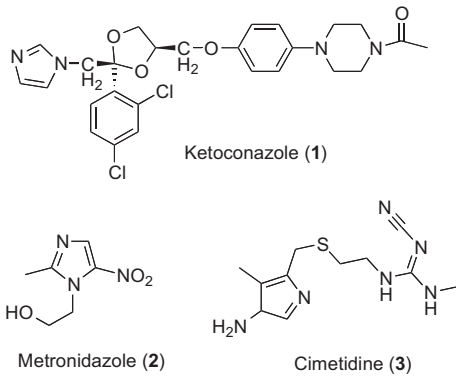

Figure 1. Medicines containing imidazole nucleus.

N-substituted imidazole derivatives are multifaceted substrates that can be utilized as a platform for the synthesis of different classes of compounds. Because of their importance, there is a continuing interest in the development of new methods for preparing them.

In this Letter, we disclose a simple and direct method for the preparation of N-substituted imidazole derivatives, via the Morita–Baylis–Hillman reaction. This process does not require an activation step. To exemplify the synthetic utility of these compounds, we also synthesized the first ionic liquids derived from MBH adducts.

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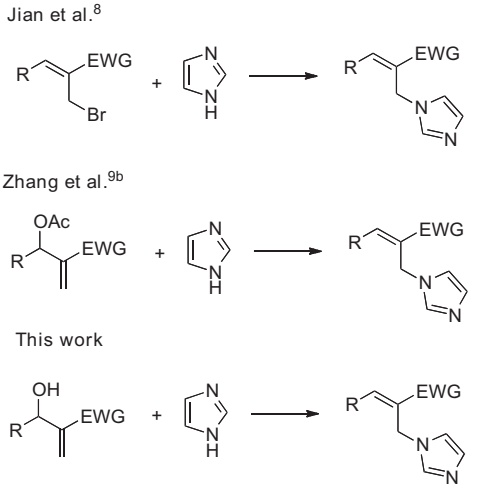


Scheme 1. Synthesis of N-substituted imidazole derivatives from Morita–Baylis–Hillman adducts.

Results and discussion

We began this work by preparing a set of Morita–Baylis–Hillman adducts using a method we have previously reported.[10] In this method, a suitable aldehyde is treated with different acrylates or cycloenones to provide the corresponding MBH adducts in good to excellent yields. The results are summarized in Table 1.

We employed the synthesized MBH adducts as substrates for the next step. We treated them with imidazole and 1,1-carbonyldiimidazole (CDI) to obtain the target compounds. CDI is commonly used in esterification reaction, and in the preparation of carbamates. However, as far as we know, it has never been tested in the presence of MBH adducts. We decided to use this reagent because it can acylate the secondary alcohol, favoring a Michael addition reaction.[11] Initially, we chose to use the mixture of solvents described by Zhang et al.[9b] and adduct **4** as a model for this study. Thus, we added adduct **4** to a mixture of THF and water (5:1), imidazole, and CDI. After 1 h, at room temperature, we obtained the desired N-substituted imidazole derivative **20** in 70% yield. We then chose to test different solvents to optimize the yield of this reaction. The results are summarized in Table 2.

Therefore, the suitable reaction condition was: 1.5 equiv of CDI, 2.0 equiv of imidazole, and acetonitrile as the solvent. (Table 2, entry 7). After 1 h, we obtained the desired imidazole derivative in very high yield at room temperature. CDI is crucial for the efficiency of this reaction. We tentatively demonstrated the role of this reagent by performing two experiments (entries 8 and 9). In the first experiment, we conducted the reaction in the absence of imidazole. After 21 h, it was possible to obtain **20** in 53% yield (Table 2, entry 8). In a second experiment, we removed CDI and ran the reaction in the presence of imidazole only. Under these conditions, we observed no product even after 48 h of stirring at room temperature.

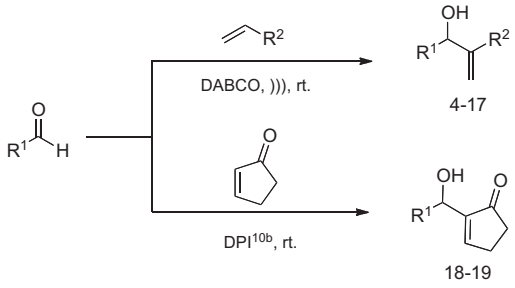
Once we optimized the conditions for this transformation, we treated adducts **5** to **19** with CDI and imidazole in acetonitrile at room temperature to give the corresponding N-substituted imidazole derivatives in good yields and high stereoselectivities. The results are summarized in Table 3.

We used ^{1}H NMR, and comparisons with data available in the literature to determine the double bond configurations of these compounds (Fig. 2).[11]

NOE experiments confirmed the *E* configuration of the double bond for almost all compounds synthesized. For example, the allylic hydrogen atoms of imidazole compound **33** (major and minor diastereoisomers) were irradiated. The results are shown in Figure 2.

The process we have developed seems to have some advantages over other processes reported in the literature. The transformation occurs directly from the MBH adducts, in a single step and does not require previous protection and/or hydroxyl activation. The N-substituted imidazole derivative results from an S_N2' reaction and its production is dependent on the presence of CDI.

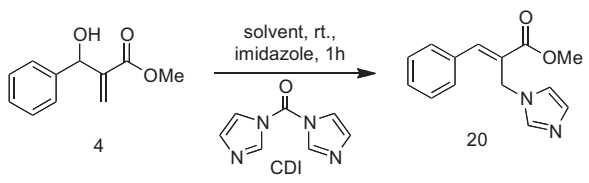
Table 1
Preparation of MBH adducts



Entry	R^1	R^2	Adducts, yield[a] (%)
1	C_6H_5	CO_2Me	**4**, 85
2	4-OBn-C_6H_4	CO_2Me	**5**, 73
3	4-*t*Bu-C_6H_4	CO_2Me	**6**, 77
4	3,5-F-C_6H_3	CO_2Me	**7**, 91
5	4-NO_2-C_6H_4	CO_2Me	**8**, 90
6	Cyclohexyl	CO_2Me	**9**, 40
7	*n*-Propyl	CO_2Me	**10**, 95
8	4-OMe-C_6H_4	CO_2Me	**11**, 71
9	3,4,5-OMe-C_6H_2	CO_2Me	**12**, 71
10	2-Thiazolyl	CO_2Me	**13**, 93
11	4-Isopropyl-C_6H_4	$CO_2{}^t$Bu	**14**, 52
12	2-Cl-Quinoloyl	CO_2Et	**15**, 93
13	4-NO_2-C_6H_4	CN	**16**, 85
14	3-OMe-C_6H_4	CN	**17**, 87
15	3-OMe-C_6H_4	—	**18**, 85
16	3-Cl-C_6H_5	—	**19**, 83

[a] Yields refer to isolated and purified products (by silica gel column chromatography).

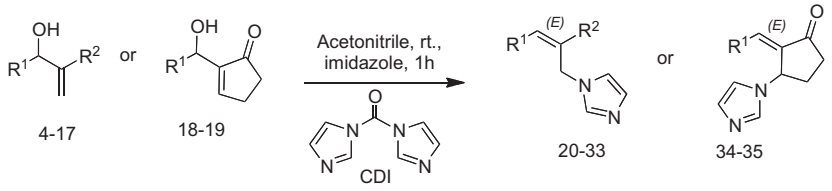
Table 2
Optimization of reaction conditions



Entry	Solvent	Conversion[a] (%)
1	THF/H_2O (5:1)	70
2	Diethyl ether	84
3	Ethyl acetate	72
4	Tetrahydrofuran (THF)	69
5	Dichloromethane	70
6	Toluene	80
7	Acetonitrile	>95
8[b]	Acetonitrile	53
9[c]	Acetonitrile	0

[a] Conversion measured by ^{1}H NMR.
[b] The reaction was carried out without the addition of imidazole (1.5 equiv CDI, rt, 21 h).
[c] The reaction was carried out in the presence of imidazole, but without CDI (2.0 equiv of imidazole, rt, 48 h).

Table 3
Synthesis of N-substituted imidazole derivatives



Entry	R^1	R^2	Products, yield[a] (%)
1	C_6H_5	CO_2Me	**20**, 83
2	4-BnO-C_6H_4	CO_2Me	**21**, 90
3	4-*t*Bu-C_6H_4	CO_2Me	**22**, 80
4	3,5-F-C_6H_4	CO_2Me	**23**, 83
5	4- NO_2-C_6H_4	CO_2Me	**24**, 70
6	Cyclohexyl	CO_2Me	**25**, 68
7	*n*-Propyl	CO_2Me	**26**, 75
8	4-MeO-C_6H_4	CO_2Me	**27**, 91
9	3,4,5-MeO-C_6H_2	CO_2Me	**28**, 73
10	2-Thiazolyl	CO_2Me	**29**, 69
11	4-Isopropyl-C_6H_4	$CO_2{}^t$Bu	**30**, 85
12	2-Cl-Quinoloyl	CO_2Et	**31**, 95
13	4-NO_2-C_6H_4	CN	**32**, 95 (*E*/*Z*; 4:1)[b]
14	3-MeO-C_6H_4	CN	**33**, 89 (*E*/*Z*; 3:1)[b]
15	3-MeO-C_6H_4	—	**34**, 72
16	3-Cl-C_6H_4	—	**35**, 75

[a] Yields refer to isolated and purified products (by silica gel column chromatography).
[b] In these cases, we also observed the presence of the *Z* diastereoisomer. The reason for this result is unclear.

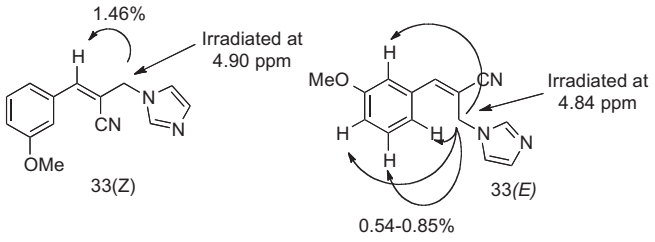
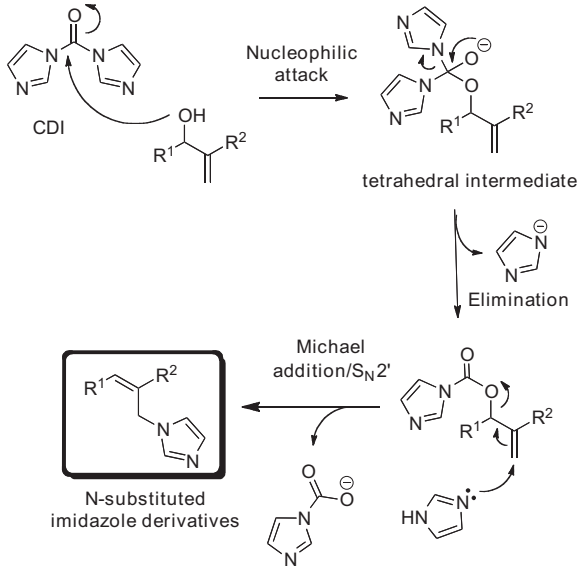
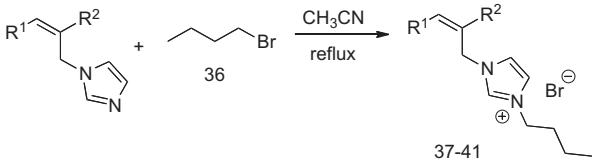


Figure 2. Confirming the *E* double bond configuration.



Scheme 2. Proposed mechanism for the preparation of N-substituted imidazole compounds with CDI.

Table 4
Ionic liquids prepared from N-substituted imidazole derivatives



Entry	R^1	R^2	Products, yield[a] (%)
1	*n*-Propyl (**26**)	CO_2Me	**37**, >95
2	3,4,5-MeO-C_6H_2 (**28**)	CO_2Me	**38**, >95
3	Thiazolyl (**29**)	CO_2Me	**39**, >95
4	4-Isopropyl-C_6H_4 (**30**)	$CO_2{}^t$Bu	**40**, >95
5	4-NO_2-C_6H_4 (**32**)	CN	**41**, 45

[a] Yields refer to isolated and purified compounds.

On the basis of the above results (Table 2 entries 7 and 8), we proposed the following mechanism for this transformation: the secondary hydroxyl group attacks the central carbonyl group of CDI, forming a tetrahedral intermediate, which results in the elimination of a molecule of imidazole. This sequence is responsible for transferring an acyl group to the hydroxyl group. The free imidazole can then participate in a Michael addition reaction, which leads to the elimination of the acyl group and the formation of the desired N-substituted imidazole derivative with high diastereoselectivity (Scheme 2).

To exemplify the synthetic versatility of these imidazole derivatives, we decided to transform a subset of them into ionic liquids. Then, we refluxed the imidazole compounds with *n*-bromobutane (**36**) in acetonitrile for 24 h to afford the corresponding ionic liquids in high yields. The results are summarized in Table 4.

All compounds tested with the exception of the cyano derivative (Table 4, entry 5) were obtained in excellent yields. We fully

characterized all new ionic liquids, and the spectra agreed with the proposed structures.

Conclusion

In summary, we report a simple and expeditious method for the synthesis of N-substituted imidazole derivatives from Morita–Baylis–Hillman adducts. In contrast to other approaches reported in the literature, no previous activation of the secondary hydroxyl group is necessary using our method. We obtained the imidazole derivatives in high yields and with good stereoselectivity.

We demonstrated the synthetic potential of these imidazole compounds by using them to prepare new ionic liquids. To the best of our knowledge, this was the first application of MBH adducts as a platform for the preparation of ionic liquids. A study aiming at the asymmetric synthesis of these new ionic liquids is ongoing and the results will be disclosed in due time.

Acknowledgments

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Supplementary data

Supplementary data (the spectra of all compounds prepared) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.146.

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