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A New Method for the Regioselective Synthesis of β-Enamino Acid Derivatives

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Key Words: Schiff bases; imines; β-enamino imidazole carbonilic derivatives; β-enamino esters; *N,N'*-carbonyl diimidazole; boron trifluoride

Abstract: A mild, simple and efficient route to β-enamino imidazole carbonilic derivatives 3 by reaction of ketimines with *N,N'*-carbonyl diimidazole in the presence of boron trifluoride as catalyst has been developed. The conversion of 3 to esters has also been explored.

Among the activated derivatives of carbonic acid, *N,N'*-carbonyl diimidazole (CDI) is one of the most effective reagents in a variety of synthetic transformations due to its reactivity, simplicity of handling and versatility.[1-4] Most of its applications are based in its ability to participate as a *transfer reagent* either of the imidazole group or of the carbonyl group. The former has mainly been used to increase the reactivity of carboxylic acids under mild conditions and their subsequent utility in the peptide synthesis [2] or in other types of system.[3] For reactions that involve its use as a carbonylating agent, the results that have appeared in the literature correspond to transfer of the CO-group with formation of carbon-*heteroatom* bonds exclusively.[4] To the best of our knowledge, only three exceptions have been reported, in which CDI is able to form carbon-carbon bonds. Thus, a simple synthesis of tetronic acid derivatives from α-hydroxyketones and CDI was reported for the first time [5a]. In the same way, Weinreb *et al.* provided, in the key step of the total synthesis of (+)-actinoboline, a second example of an intramolecular process with one carbonyl-carbon bond formation.[5b] More recently, we have described a new method of synthesis of 4(1*H*)-pyridones from 2-aza-1,3-dienes and CDI through the formation, in an intermolecular process, of two new carbonyl-carbon bonds.[6] In sharp contrast with the above results, very little is known about the ability of CDI to *transfer* both carbonyl and imidazole groups simultaneously.

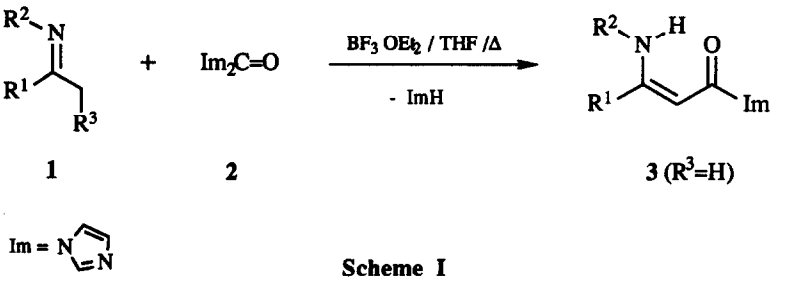
β-Enamino acid derivatives,[7] particularly β-enamino esters, are important building blocks in organic synthesis. Among the several methods of preparation of these systems, a two step sequence starting from carbonyl compounds *via C*-alkoxycarbonylation of enolate anions, followed by condensation of the β-keto ester thus obtained with ammonia or amines, appears to be the most practical and frequently employed procedure.[8]

However, the success of this approach requires a strict control of the reaction conditions in order to ensure

effective *C*-regioselectivity [9] and, in most instances, it is also highly dependent on the nature of starting materials.[9,10] In this context, it is worth noting that a mild and convenient procedure for the preparation of β-keto esters starting from reactive imidazolides (resulting from treatment of carboxylic acids with CDI) and neutral nucleophilic magnesium enolates has been described.[11] In contrast, the synthesis of β-enamino acids and related reactive derivatives appears to be rather difficult. This could be due to their instability since normally they hydrolyse on work-up to give the parent keto ester.

Therefore, we wish to report here the behaviour of CDI as a *transfer reagent* of the "CO-Im" grouping in its reaction with Schiff bases and the application of this methodology to the synthesis of β-enamino acid derivatives.

Thus, when ketimines **1**(1.0 eq.) were treated with *N,N'*-carbonyl diimidazole (CDI) **2** (1.3 eq.) in tetrahydrofuran (THF) at 60°C for 12 h. and in the presence of BF_3 OEt_2 (1.0 eq.), β-enamino carbonyl imidazole derivatives **3** [12] were obtained in good to excellent yields after aqueous workup (**Scheme I**). The results of this study are summarized in **Table 1** and they indicate that the reaction occurs with total regioselectivity, the *C*-carbonyl imidazole derivative **3** being the sole isolated product.



1 **2** **3** (R^3=H)

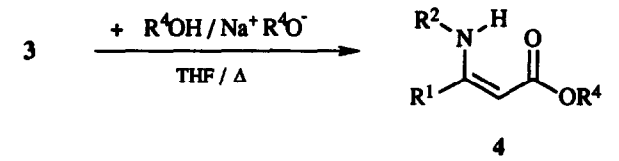
Im =

Scheme I

As mentioned above, compounds **3** were obtained by the use of BF_3 OEt_2 as catalyst. When a similar treatment was carried out in the presence of other Lewis acids or in absence of catalyst the starting materials were recovered. It must be emphasized that the best chemical yields have been obtained when the reaction is carried out in THF as solvent [13] and the CDI is allowed to react first with the catalyst, because the complex thus obtained (CDI→BF_3) increases the reactivity of CDI toward the ketimines **1**.

The course of the reaction is markedly affected not only by the Lewis acid but also by the nature of the substituents on the initial ketimines. As shown in **Table 1**, the process is rather general as regards the amine residue in **1**; however, only methyl ketimines **1** (R^3=H) have so far shown a tendency to react with CDI. Thus, whereas compounds **1** (R^3=H) were easily and directly converted into **3**, no reaction was observed under the same conditions with ketimines **1** in which $R^3 \neq H$ (see entry 7, **Table 1**). This aspect, however, is of great utility when the reaction is carried out with unsymmetrical alkyl methyl ketimines. In this case, only the product corresponding to regioselective C-C formation by the methyl group was obtained (see entry 6, **Table1**).

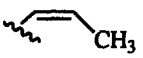
To demonstrate the utility of this process, the behaviour of **3** toward alcohols was examined as is outlined in **Scheme II**. The β-enamino imidazolide **3** was treated with a slight excess of alcohol in the presence of sodium alkoxide in refluxing THF for 2-6 hours to afford the corresponding β-enamino esters **4** in high yields.[12] Representative results for this process are shown in **Table 1** (entries 8-12), and from this data it can be asserted that the reaction is quite general and applicable to all kind of alcohols, including tertiary ones.[3a]



Scheme II

In order to simplify the method, we tried to obtain **4** directly from ketimines **1** without isolation of the derivatives **3**. This "one pot" procedure takes place successfully under the same reaction conditions as described above, but with lower chemical yields for **4** (<40 based on **1**). Moreover, side products such as ketones resulting from the hydrolysis of the starting ketimines **1** and other unidentified products were also present.

Table 1 β-Enamino acid derivatives **3** and **4** obtained from CDI (**2**)

Entry	Compound [a]	R^1	R^2	R^4	Yield (%)	m.p.[b] (°C)
1	**3a**	Ph	Ph	—	84	146-8
2	**3b**	Ph	*n*-C_4H_9	—	73	oil [c]
3	**3c**	Ph	(±)-Ph(CH_3)CH	—	69	oil [c]
4	**3d**	Ph		—	88	141-3
5	**3e**	*p*-$C_2H_5O_2CC_6H_4$	*c*-C_6H_{11}	—	79	oil [c]
6	**3f**	C_2H_5	*p*-$CH_3C_6H_4$	—	51	oil [c]
7	**3g** (R^3=CH_3)	Ph	Ph	—	No reaction	—
8	**4a**	Ph	Ph	CH_3	94	84-6
9	**4b**	Ph	Ph	*i*-C_3H_7	71	81-3
10	**4c**	Ph	Ph	*t*-C_4H_9	75	oil [c]
11	**4d**	Ph	*n*-C_4H_9	$PhCH_2$	88	oil [c]
12	**4e**	Ph	(±)-Ph(CH_3)CH	CH_2=$CHCH_2$	76	oil [c]

[a] R^3=H, except entry 7; [b] Melting points are uncorrected; [c] Purified by flash chromatography.

Acid hydrolysis of **3** (H_2SO_4 2N/THF/60°C/2h) led to the corresponding methyl ketone R^1COCH_3, probably by decarboxylation of the initially formed β-keto acid. On the contrary, the acid hydrolysis of **4** yielded mainly β-keto esters.

In summary, the first route to enamino acid derivatives **3** and **4** directly from CDI and ketimines has been described. Further work on the scope of these reactions is in progress.

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12. All new compounds exhibited ^{1}H, ^{13}C NMR and mass spectra consistent with the assigned structure. For example: **3a**, $C_{18}H_{15}N_3O$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 5.5 (s, 1H), 6.8-7.4 (m, 11H), 7.5 (br s, 1H), 8.3 (br s, 1H), 11.5 (br s, 1H NH);^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 164.3 (C), 163.8 (C), 138.5 (C), 134.8 (C), 130.1 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 124.8 (CH), 123.4 (CH), 115. 8 (CH), 87.8 (CH) ; MS *m/e*, 289 (M^+), 222 (100%); **3b**, $C_{16}H_{19}N_3O$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 0.9 (t, 3H), 1.3 (m, 2H), 1.6 (m, 2H), 3.2 (q, 2H), 5.1 (s, 1H), 7.0 (br s, 1H); 7.4-7.6 (m, 6H), 8.1 (br s, 1H), 10.0 (br s, 1H NH); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 168.6 (C), 163.0 (C), 135.0(C), 134.5 (CH), 129.5 (CH), 129.4 (CH), 128.3 (CH), 127.0 (CH), 115.4 (CH), 83.2 (CH), 44.3 (CH_2), 32.1 (CH_2), 19.2 (CH_2), 13.1 (CH_2); MS *m/e*, 269 (M^+), 202 (100%); **3e**, $C_{21}H_{25}N_3O_3$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1.1-1.9 (m, 10H), 1.4 (t, 3H), 3.2 (m, 1H), 4.4 (q, 2H), 5.1 (s, 1H), 7.0 (br s, 1H), 7.5 (d, 2H), 7.5 (br s, 1H), 8.2 (d, 2H), 8.2 (br s, 1H), 10.0 (br d, 1H NH); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 166.2 (C), 165.0 (C), 162.9 (C), 138.8 (C), 131.2 (C), 129.3 (CH), 126.8 (CH), 115.2 (CH), 83.4 (CH), 60.7 (CH_2), 52.6 (CH), 33.5 (CH_2), 24.4 (CH_2), 23.6 (CH_2), 13.7 (CH_3) ; MS *m/e*, 367 (M^+), 300 (100%).

    4b, $C_{18}H_{19}NO_2$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1,3 (d, 6H), 5.0 (s, 1H), 5.2 (m, 1H), 6.7-7.4 (m, 10H Ar), 10.3 (br s, 1H NH); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 169.5 (C), 158.7 (C), 140.3 (C), 135.9 (C), 129.2 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 122.7 (CH), 121.9 (CH), 91.7 (CH), 66.2 (CH), 22.0 (CH_3); MS *m/e*, 281 (M^+), 194 (100%); **4c**, $C_{19}H_{21}NO_2$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1.5 (s, 9H), 4.9 (s, 1H), 6.6-7.3 (m, 10H Ar), 10.3 (br s, 1H NH);^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 169.8 (C), 158.1 (C), 140.5 (C), 136.1 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 122.5 (CH), 121.9 (CH), 93.1 (CH), 79.2 (C), 28.4 (CH_3); MS *m/e*, 295 (M^+), 193 (100%); **4e**, $C_{20}H_{21}NO_2$: ^{1}HNMR ($CDCl_3$, TMS, 300 MHz) δ 1.4 (d, 3H), 4.4 (m, 1H), 4.6 (m, 2H), 4.6 (s, 1H), 5.2 (dt, 1H, *J*=10.4 Hz *J*=1.4 Hz), 5.3 (dq, 1H, *J*=17.2 Hz *J*=1.5 Hz), 6.0 (m, 1H), 6.9-7.4 (m, 10H Ar), 8.9 (br d, 1H NH); ^{13}CNMR ($CDCl_3$, TMS, 75 MHz) δ 169.5 (C), 164.2 (C), 144.4 (C), 136.0 (C), 133.1 (CH), 128.8-125.3 (CH), 116.8 (CH_2), 86.1 (CH), 63.3 (CH_2), 53.5 (CH), 24.3(CH_3); MS *m/e*, 307 (M^+), 105 (100%).
13. A variety of solvents were examined; tetrahydrofuran was found to be the best. Other solvents such as ether, toluene or CH_2Cl_2 gave no significant amount of **3**.

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