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Switchable Reactivity of Acylated α,β-Dehydroamino Ester in the Friedel−Crafts Alkylation of Indoles by Changing the Lewis Acid

Elena Angelini, Cesarino Balsamini, Francesca Bartoccini, Simone Lucarini, and Giovanni Piersanti*

Institute of Medicinal Chemistry, University of Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino (PU), Italy

giovanni.piersanti@uniurb.it

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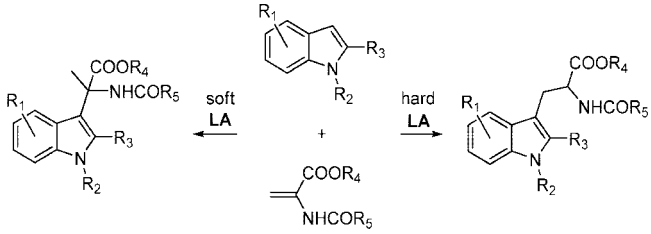

Highly regioselective electrophilic substitution of indoles with *N*-acetylated α,β-dehydroalanine methyl ester, promoted by different transition metal salts was achieved. The orthogonal regioselectivity provides an efficient protocol toward highly functionalized 3-indolyl-α-amino acids. The mechanism of the reactions was explored by NMR studies.

Amino acids and their derivatives are well-known as versatile building blocks for pharmaceutical applications, as well as essential starting material for the generation of molecular diversity.[1] Therefore, we have focused our attention on developing methodologies to generate nonproteinogenic amino acids,[2] using readily available *N*-protected dehydroamino esters, such as dehydroalanine.

The amino acid dehydroalanine (Dha) is found in a number of proteins and nonribosomal natural products, and is typically revealed by the activation and β-elimination of serine or cysteine.[3] α,β-Unsaturated amino acids can alter the conformation, rigidity, and proteolytic susceptibility of the polypeptide backbone.[4] Intra- or intermolecular electrophilic Michael addition with these unsaturated residues can lead to the formation of Dha adducts, including intramolecular lanthionine cross-links.[5]

The indole nucleus is found in a number of biologically active natural and unnatural compounds, and the synthesis of its derivatives continues to be an intriguing subject in organic synthesis.[6] Friedel−Crafts (F-C) alkylation of indoles with an α,β-unsaturated carbonyl compound such as the Michael acceptor is a straightforward approach for the synthesis of substituted indoles. Several conjugate additions of indoles to various Michael acceptors, some of which are highly enantioselective, have been developed by using either Lewis acids (LA) or organic catalysts.[7]

Although remarkable achievements have been made using the F-C alkylation of indole substrates with α,β-unsaturated carbonyl compounds, to the best of our knowledge there have been no reports in which *N*-acylated dehydroamino esters (α-amidoacrylates) have been employed.

The potential value of the *N*-acyl-α,β-dehydroamino esters in synthetic chemistry is derived mainly from their ready availability and unique reactivity.[8] The contemporary presence of acylamino and ester groups on the same carbon of the double bond can promote the nucleophilic attack at the α and β positions (Figure 1), providing α-amino acids that can be readily transformed into a range of different functionalities, or even

* Address correspondence to this author. Fax: +39-0722-303313. Phone: +39-0722-303320.

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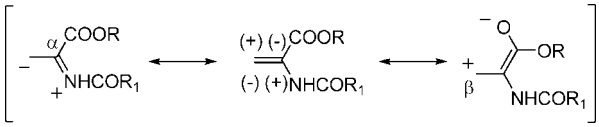


FIGURE 1. Contributing structures of α,β-dehydroamino esters.

more importantly they can be resolved by asymmetric hydrolysis with use of α-chymotrypsin or carboxypeptidase A.[9]

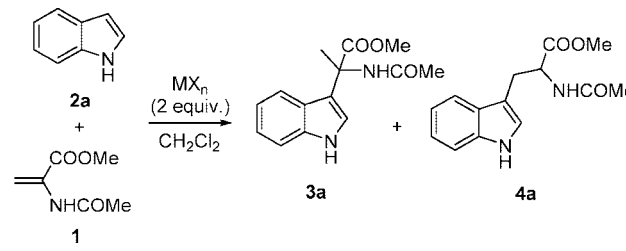
In this paper, we document the first efficient regioselective LA-promoted addition of indoles to methyl α-methylacetamidoacrylate (**1**),[10] one of the simplest compounds of the *N*-acyl-α,β-dehydroamino ester family. The procedure is straightforward and allows rapid access to a broad range of 3-indolyl-α-amino acids derivatives. In particular, the successful regioselective activation strategy to enester-enamide substrate **1** was achieved by appropriate choice of LA in terms of hardness and softness.[11]

The proposed F-C alkylation strategy was first examined by reacting indole with **1** in the presence of a series of LAs in dichloromethane for 2 h. (Table 1). Using a catalytic amount or less than 1 equiv of the highly reactive and commercially available LA $EtAlCl_2$ in hexane solution did not provide any of the desired substituted indole product. When the reaction was carried out with 1 equiv of $EtAlCl_2$, the yield was low (Table 1, entry 1). The presence of 2 equiv of $EtAlCl_2$ was required to obtain *N*-acetyl tryptophan methyl ester **4a** in high yield as the only regioisomer (Table 1, entry 2). Higher temperatures gave lower yields, most likely due to polymerization (Table 1, entry 4).

The effects of various other LAs belonging to the aluminum group such as BF_3, $GaCl_3$, and $InCl_3$ were also studied, but they were found to be ineffective for this conversion (Table 1, entries 5−8). Although $LiClO_4$,[12] $MgBr_2$,[13] and $Sc(OTf)_3$[14] are known to be efficient catalysts for F-C and for Michael addition reactions, surprisingly they showed no reactivity in our system (Table 1, entries 9−11). Compound **4a** was obtained in low yield when $TiCl_4$ was employed using the same conditions (Table 1, entry 12). Instead, we were delighted to find that $ZrCl_4$, a safe, economical, and environmentally benign LA,[15] furnished the desired product in good yield even though a longer reaction time was needed (Table 1, entry 13).

Next, we explored late transition metal salts with more azaphilic/soft characteristics as the LAs under similar reaction conditions. Using $ReCl_5$, $NaAuCl_4 \cdot 2H_2O$, and $Bi(OTf)_3$, we obtained complete regioselectivity to provide the other isomer **3a** in good yield (Table 1, entries 14, 16, and 19). The indole nucleus preserved C3 regioselectivity while **1** no longer behaved as an electron-deficient olefin but as an enamide, performing

TABLE 1. Effect of LA in the F−C Reaction of 1 and Indole



entry	MXn	*T* (°C)	yield (%)	**3a/4a**
1[a]	$EtAlCl_2$	0	10	0/100
2	$EtAlCl_2$	0	75	0/100
3[b,e]	$EtAlCl_2$	0	58	0/100
4[b]	$EtAlCl_2$	83	50	0/100
5	$BF_3 \cdot OEt_2$	0	NR[c]	
6	$GaCl_3$	rt	NR[c]	
7[d]	$InCl_3$	rt	NR[c]	
8	$InCl_3$	0	NR[c]	
9	$LiClO_4$	rt	NR[c]	
10	$MgBr_2$	rt	NR[c]	
11	$Sc(OTf)_3$	rt	NR[c]	
12[e]	$TiCl_4$	rt	30	0/100
13[f]	$ZrCl_4$	0	65	0/100
14[e]	$ReCl_5$	rt	55	100/0
15	$IrCl_4$	rt	NR[c]	
16[e]	$NaAuCl_4 \cdot 2H_2O$	rt	46	100/0
17	$Cu(OTf)_2$	rt	NR[c]	
18	$Zn(OTf)_2$	rt	NR[c]	
19[e]	$Bi(OTf)_3$	rt	62	100/0
20	CF_3SO_3H	0	NR[c]	
21[g]	HCl	0	NR[c]	
22	Amberlyst	0	NR[c]	
23	Montmorillonite	0	NR[c]	

[a] 1 equiv of LA was used. [b] 1,2-Dichloroethane was used as a solvent. [c] No reaction occurred. [d] H_2O/THF 9:1 mixture was used as a solvent. [e] The reaction was carried out for 4 h. [f] The reaction was carried out for 24 h. [g] 4 M HCl solution in dioxane was used.

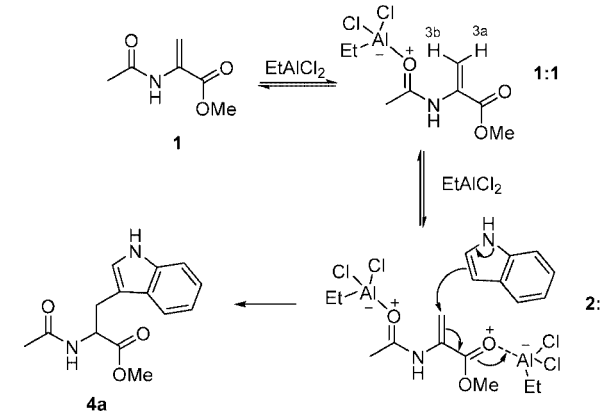


FIGURE 2. Plausible reaction mechanism of **1** and indole catalyzed by 2 equiv of $EtAlCl_2$.

the α-amidoalkylation reaction (Figure 3). Rhenium pentachloride is very air and moisture sensitive making it unattractive for use in synthetic organic chemistry. Similarly, the relatively high cost and toxicity preclude the use of gold compounds in stochiometric amount, although catalysis by gold compounds has rapidly become a hot topic in chemistry.[16] On the other hand, bismuth compounds have recently attracted attention due to their low cost, ease of handling, and remarkably low toxicity, rendering them suitable for green chemistry.[17] Among the metal salts tested $IrCl_4$, $Cu(OTf)_2$, and $Zn(OTf)_2$ were found to be ineffective (Table 1, entries 15, 17, and 18). No reaction

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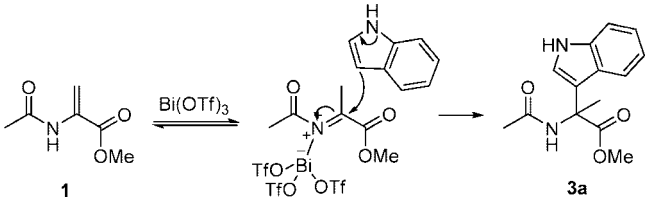


FIGURE 3. Plausible reaction mechanism of **1** and indole catalyzed by 1 equiv of $Bi(OTf)_3$.

occurred with Brönsted acids triflic acid or hydrogen hydrochloride, nor heterogeneous LAs such as Amberlyst or montmorillonite (Table 1, entries 20−23).

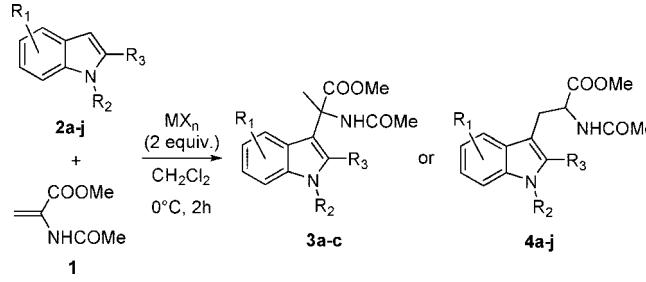
To explain the switchable regioselectivity of the reaction by changing the characteristics of the LA, we carried out ^{1}H NMR experiments. First, we examined the Michael addition reaction (β-regioselectivity) performed with $EtAlCl_2$. The ^{13}C NMR experiments reported by Avenoza et al.[18] and our ^{1}H NMR experiments (see the Supporting Information) suggest that the nucleophilic oxygen of the amide is the coordination site of the metal without activating the electron-deficient alkene. In the $EtAlCl_2$:1 complex (1:1) spectrum we observed line broadening of the H_{3b}, methyl amide, and NH signals (Figure 2) due to rapid chemical exchange between the free and bonded substrate. These changes provide further evidence of aluminum coordination of the amide carbonyl. A similar study on the $EtAlCl_2$:1 complex (2:1) showed the broadening of all the protons. These facts can be interpreted in terms of coordination of the second equivalent of $EtAlCl_2$ to the ester carbonyl oxygen, which probably causes a decrease in the LUMO energy of this olefin and therefore makes the reaction more effective (Figure 2).

Second, regarding the α-regioselective addition (product **3a**), we imagined that the more azaphilic LA initially facilitates the tautomerization of enamide to *N*-acylimine, with the latter reacting with indole. A similar intermediate already has been proposed in the Brönsted acid-catalyzed enantioselective F-C reaction of indoles and α-arylenamides.[19] To obtain insight into the reaction mechanism, we performed a ^{1}H NMR experiment on the $Bi(OTf)_3$:1 complex (1:1) (see the Supporting Information). The spectrum showed the full conversion of the olefinic protons to three singlets corresponding to the three methyl groups of the *N*-acylimine tautomer (Figure 3). Clearly, the more azaphilic LA plays an important role in the inversion of the regioselectivity of the F-C reaction.

It is noteworthy that while enamides have generally been used as nucleophiles in acid-catalyzed reactions, compound **1** plays the role of the electrophile in this reaction system with indoles. Remarkably, this represents an easy route to unnatural α-amino acids containing quaternary carbon centers bearing a nitrogen atom (α,α-disubstituted glycine). Therefore, the present activation mode is regarded as an efficient alternative to the generation of aliphatic *N*-acylimines, which are generally labile and difficult to isolate.

To demonstrate the scope and potential of the present reaction, we next examined a series of indole derivatives **2a**−**j** with **1** under the optimal reaction conditions (Table 2). All the substituted indole derivatives underwent the F-C reaction smoothly to give the corresponding β-substituted alanines (**4a**−**j**) in good to excellent yields. The presence of a substituent either on the indole nitrogen ring or on the aromatic ring did not affect the Michael addition. With regard to the substituent effect on the indole ring, neither electron-donating groups (Table 2, entries 6 and 9) nor electron-withdrawing groups (Table 2, entries 7, 8, and 10) on the indole affected the efficiency of the reaction. In addition, *N*-methylindole, as well as indoles substituted with methyl and phenyl group in the 2 position, provided the desired products (Table 2, entries 2−5).

TABLE 2. Substrate Scope for the F-C Reaction



entry	indole	MX_n	product	yield (%)
1	indole (**2a**)	$EtAlCl_2$	**4a**	75
2	*N*-methylindole (**2b**)	$EtAlCl_2$	**4b**	60
3	2-methylindole (**2c**)	$EtAlCl_2$	**4c**	66
4	2-phenylindole (**2d**)	$EtAlCl_2$	**4d**	52
5	*N*-methyl-2-methyl indole (**2e**)	$EtAlCl_2$	**4e**	35
6	5-methoxyindole (**2f**)	$EtAlCl_2$	**4f**	77
7	5-bromoindole (**2g**)	$EtAlCl_2$	**4g**	65
8	5-fluoroindole (**2h**)	$EtAlCl_2$	**4h**	80
9	4-methoxyindole (**2i**)	$EtAlCl_2$	**4i**	63
10	6-chloroindole (**2j**)	$EtAlCl_2$	**4j**	57
11	indole (**2a**)	$Bi(OTf)_3$	**3a**	62
12	*N*-methylindole (**2b**)	$Bi(OTf)_3$	**3b**	50
13	5-bromoindole (**2g**)	$Bi(OTf)_3$	**3c**	61

In conclusion, we have developed for the first time an efficient reaction between α-amidoacrylates and indoles in the presence of transition metal salts where the regioselectivity outcome can be modulated by tuning the oxo- and aza-philic nature of the LA. The process highlights the use of α,β-dehydroamino acids as versatile substrates in C−C bond forming reactions, opening new opportunities for applications in synthesis and biology. The reaction was even further extended to include several monosubstituted indoles and was applied to the synthesis of different natural and unnatural tryptophanes.

Experimental Section

A Typical Procedure for the Preparation of 3-Tryptophane Derivatives (4a−j). A 1 M solution of $EtAlCl_2$ in hexane (2 mmol, 2 mL) was added dropwise to a stirred and cooled (0 °C) mixture of methyl 2-acetamidoacrylate **1** (143 mg, 1 mmol) and indole (**2a**) or substituted indoles **2b**−**j** (1,5 mmol) in dry CH_2Cl_2 (4 mL) under a nitrogen atmosphere. The mixture was stirred at 0 °C for 2 h, then carefully poured into an ice-cold saturated aqueous sodium hydrogen carbonate solution (10 mL). The resulting suspension of $Al(OH)_3$ was filtered through Celite and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (column size: 15 × 1.5 cm^2) on silica gel to give the product **4a**−**j**. For compound **4b**: TLC (EtOAc 100%), R_f 0.49 (UV, CAM); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.97 (s, 3H, $NHCOCH_3$), 3.30 (dd, 2H, J_1 = 5.3 Hz, J_2 = 1.1 Hz, CH_2), 3.71 (s, 3H, $COOCH_3$), 3.75 (s, 3H, NCH_3), 4.89−4.98 (m, 1H, CH), 5.98 (br d, 1H, J = 7.5

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Hz, $NHCOCH_3$), 6.83−7.53 (m, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 169.6, 136.7, 128.1, 127.2, 121.6, 119.0, 118.4, 109.2, 108.3, 53.0, 52.1, 32.5, 27.3, 23.0; FTIR (CH_2Cl_2) ν_{max}/cm^{-1} 3293 (br), 2951 (m), 1743 (s), 1655 (s), 1545 (s); MS (ESI) 275 (M + 1). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.69; H, 6.62; N, 10.22.

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Supporting Information Available: Experimental procedures, characterization, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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