Improved Protocol for the Three-Component *Biginelli* Reactions and *Biginelli*-Like *Mannich* Reactions of Carbamates, Aldehydes, and Ketones

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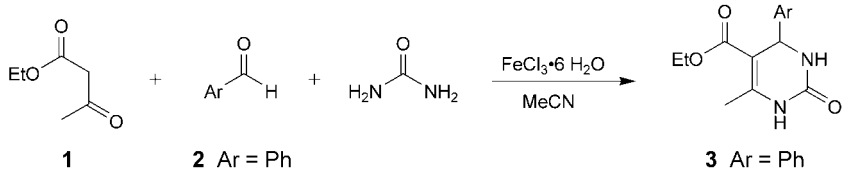
A mild, convenient, and improved method for the direct three-component *Biginelli* and *Biginelli*-like *Mannich*-type reactions of carbonyl compounds in the presence of inexpensive $FeCl_3 \cdot 6\ H_2O$ and Me_3SiCl as catalysts is described. Reactions performed with carbamates can be used to directly access *N*-protected *β*-amino carbonyl compounds in a single step.

Introduction. – In past decades, $FeCl_3 \cdot 6\ H_2O$ has been used as an extremely efficient catalyst for *Michael* reactions of *β*-keto esters with both enones and vinyl ketones [1]. Recently, we found that $FeCl_3 \cdot 6\ H_2O$ is also an efficient catalyst for aza-type *Michael* reactions of carbamates and aromatic amines [2]. Inspired by these results and previous findings, we thought that this *Lewis* acid might also be an efficient catalyst for three-component *Biginelli* reactions [3] and related *Biginelli*-like *Mannich* reactions under mild conditions. Here, we present our latest results concerning these types of simple and efficient transformations.

Results and Discussion. – When $FeCl_3 \cdot 6\ H_2O$, in the presence of Me_3SiCl (TMSCl; 0.5 equiv.), was used as a catalyst in the three-component *Biginelli* reaction of acetoacetate (=ethyl 3-oxobutanoate; **1**), benzaldehyde (**2**, Ar = Ph), and urea in a ratio of 1:1:1.5, dihydropyrimidinecarboxylates of type **3** were produced within a few hours in moderate-to-high yields of 71–87% (*Scheme 1*). Thereby, both electron-poor and electron-rich aromatic aldehydes proved to be reactive. In contrast, the original method [4] with $FeCl_3 \cdot 6\ H_2O$ requires much higher temperatures for the reaction to proceed.

Scheme 1. *Typical* Fe^{III}*-Catalyzed* Biginelli *Reaction*



1 **2** Ar = Ph **3** Ar = Ph

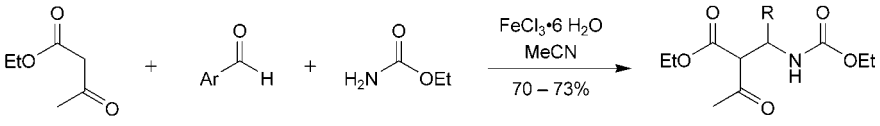
In an extension of the program to discover versatile routes to novel *Biginelli* scaffolds, we had discovered that the amide moiety of carbamates can also be reacted,

offering a simple route to β-amino carbonyl compounds [5]. The latter constitute biologically important natural products and serve as versatile intermediates for the synthesis of N-containing compounds [6]. The development of novel synthetic methods leading to β-amino ketones, β-amino acids and their derivatives has, thus, attracted much attention among organic chemists [7].

Mannich-type reactions are established, powerful methods for the synthesis of β-amino carbonyl compounds [8]. To avoid the typical disadvantages of *Mannich* reactions, *direct* approaches based on the use of aldehydes, amines, and ketones have been developed in the past few years [9–12].

Our protocol for *Biginelli*-like three-component *Mannich* condensations is based on the use of carbamates instead of amines: a mixture of the three components, *i.e.*, aldehyde, acetoacetate, and carbamate, in a ratio of 1:1:1.5, is reacted in the presence of $FeCl_3 \cdot 6\ H_2O$ (0.2 equiv.) and TMSCl (0.5 equiv.) at room temperature in MeCN for *ca.* 12 h, giving rise to *N*-protected β-amino carbonyl compounds of type **4** in 70–73% yield (*Scheme 2*). To the best of our knowledge, there is only one example of a similar direct *Mannich* reaction in the literature [13], and this reaction was carried out at reflux temperature over a longer period of time (3 d).

Scheme 2. *Three-Component* Biginelli-*Like* Mannich *reaction*



1 **2**

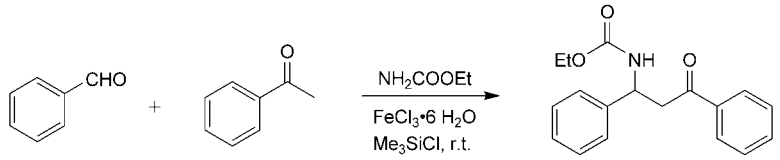
4a R = C_6H_5
4b R = 4-Cl-C_6H_4
4c R = 4-Me-C_6H_4

To optimize the conditions for the three-component *Mannich* reaction between aldehydes, ketones, and carbamates, we investigated the model reaction between benzaldehyde, acetophenone, and ethyl carbamate (*Table 1*). In the absence of TMSCl (*Entry 6*), no product **5** was formed after 16 h. Thus, the combined use of $FeCl_3 \cdot 6\ H_2O$ and TMSCl is crucial for the room-temperature *Mannich* reaction with carbamates. The role of TMSCl is not completely understood, but may be rationalized in terms of *Lewis* acid acitvation of the C=O group [14].

It should be noted that the above direct *Mannich* reaction can also be carried out with anhydrous $FeCl_3$ instead of $FeCl_3 \cdot 6\ H_2O$. However, the anhydrous reagent is not stable in air and is considerably more expensive.

The key to the success of the reaction lies in the choice of solvent and the ratio of reagents. A 1:1:1.5 ratio of benzaldehyde/acetophenone/ethyl carbamate, with 10 mol-% of $FeCl_3 \cdot 6\ H_2O$ and 0.5 mol-% of TMSCl gave the adduct **5** in moderate yield (*Table 1*, *Entries 1* and *2*). In toluene at elevated temperature (80°), only 12% of **5** were isolated (*Entry 3*). Interestingly, when 5.0 instead of 1.5 equiv. of carbamate was used, the yield rose from 55 to 67% (*Entries 2 vs. 4*). We also found that the *Mannich* reaction was strongly influenced by solvent. When a CH_2Cl_2/Et_2O 1:1 mixture was used instead of CH_2Cl_2 alone, a significant improvement in yield was observed (*Entry 5*).

Table 1. *Fe^{III}-Catalyzed Three-Component* Mannich-*Type Reaction of Benzaldehyde, Acetophenone, and Ethyl Carbamate*. Conditions: 0.1 equiv. of $FeCl_3 \cdot 6\ H_2O$, 0.5 equiv. of Me_3SiCl (see *Exper. Part.*).

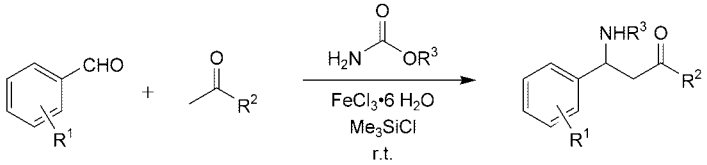


Entry	Substrate ratio[a])	Solvent	*t* [h]	*T* [°]	Yield [%][b])
1	1 : 1 : 1.5	CH_2Cl_2	6	25	40
2	1 : 1 : 1.5	CH_2Cl_2	12	25	55
3	1 : 1 : 1.5	Toluene	2	80	12
4	1 : 1 : 5.0	CH_2Cl_2	12	25	67
5	1 : 1 : 1.5	CH_2Cl_2/Et_2O 1 : 1	12	25	75
6	1 : 1 : 5.0[c])	CH_2Cl_2	16	25	0
7	1 : 1 : 1.5[d])	CH_2Cl_2	24	25	0

[a]) Aldehyde/ketone/carbamate. [b]) After chromatographic purification. [c]) Without Me_3SiCl. [d]) HCl was used as a catalyst.

To gain deeper insight into the scope and limitations of this method, several electron-rich and electron-poor benzaldehydes and ketones were used as substrates, along with different N-containing nucleophiles. The results are collected in *Table 2*. Again, electron-rich as well as electron-poor benzaldehydes afforded the corresponding *Mannich*-type adducts in moderate to good yields.

Table 2. *Fe^{III}-Catalyzed Three-Component* Mannich-*Type Reaction with Different Aldehydes, Ketones, and Carbamates as Substrates*. Conditions: aldehyde (5 mmol), carbamate (10 mmol), ketone (5 mmol), $FeCl_3 \cdot 6\ H_2O$ (0.5 mmol), Me_3SiCl (2.5 mmol), CH_2Cl_2/Et_2O 1 : 1, r.t., 15 h.



Entry	R^1	R^2	R^3	Yield [%][a])
1	H	4-$(NO_2)C_6H_4$	Et	45[b])
2	H	C_6H_5	Bn[c])	72
3	4-Br	C_6H_5	Bn	73
4	4-Cl	4-$(NO_2)C_6H_4$	Et	56[b])
5	4-Cl	C_6H_5	Et	68
6	4-Me	C_6H_5	Et	71
7	2-Cl	C_6H_5	Et	60

[a]) After chromatographic purification. [b]) Conditions: aldehyde (1 mmol), ketone (5 mmol), carbamate (2 mmol), $FeCl_3 \cdot 6\ H_2O$ (0.1 equiv.), Me_3SiCl (0.5 equiv.), $CHCl_3/Et_2O$ 1 : 1, r.t., 24 h. [c]) Bn = Benzyl.

In summary, a mild, convenient, and inexpensive variant of the three-component *Biginelli* reaction has been developed, based on an Fe^{III}/Me_3SiCl catalytic system. The new protocol can be used to react either ureas or carbamates with different electron-rich or electron-poor aromatic aldehydes and ketones, giving rise to dihydropyrimidines or open-chain β-amino carbonyl compounds, respectively. Our experiments, thus, extend the versatility of N-containing weak nucleophiles in *Mannich* reactions. Further studies concerning the mechanism of and potential asymmetric catalysts for these types of reactions are now under investigation.

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Experimental Part

General. All solvents and reagents were purchased and used without further purification. TLC: Silica-gel (F_{254}) plates; spots visualized under UV light. Flash chromatography (FC): silica gel (100–200 mesh). IR Spectra: FT-IR apparatus; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: at 400 and 100 MHz, resp., and were referenced to internal solvent signals; δ in ppm, J in Hz. All compounds were characterized spectroscopically and by GC/MS (*Agilent 6890N GC/5973N MS*, *HP-5 MS*).

General Procedure for the Direct Mannich *Reaction of Carbamates.* To a soln. of the aldehyde (5.0 mmol) and $FeCl_3 \cdot 6\ H_2O$ (0.5 mmol) in Et_2O (10 ml) were added, in this order, ethyl carbamate (10 mmol) in CH_2Cl_2 (10 ml), the ketone (5.0 mmol), and Me_3SiCl (0.5 equiv.). The mixture was stirred untill the reaction was complete (TLC). The reaction was quenched with H_2O, and the aq. layer was extracted with $CHCl_3$. The combined org. layers were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by FC (AcOEt/petroleum ether), and all products were fully characterized.

Selected Data for Ethyl N-*[1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl]carbamate* (*Table 2*, *Entry 7*). IR: 3313, 3071, 2981, 2908, 1693, 1579, 1551, 1349, 1268, 1239, 1064, 1033. ^1H-NMR: 7.88 (*d*, $J = 7.2$, 2 H); 7.57 (*m*, 1 H); 7.41 (*m*, 2 H); 7.24 (*m*, 2 H); 6.81 (*m*, 2 H); 5.63 (br. *s*, 1 H); 5.22 (*dd*, $J = 6.4$, 14.0, 1 H); 4.07 (*dd*, $J = 6.8$, 14.0, 2 H); 3.64–3.74 (*m*, 2 H); 3.37–3.43 (*m*, 1 H); 1.20 (*t*, $J = 6.4$, 15.2, 3 H). ^{13}C-NMR: 198.2; 159.0; 156.1; 136.9; 133.7; 133.6; 128.9; 128.3; 127.8; 114.2; 61.1; 55.5; 51.5; 44.3; 14.8. Anal. calc. for $C_{18}H_{18}NO_3Cl$: C 65.16, H 5.43, N 4.22; found: C 65.12, H 5.41, N 4.25.

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