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Iron(III) chloride-catalyzed mechanochemical cascade synthesis of highly-substituted pyrrolyl indoles

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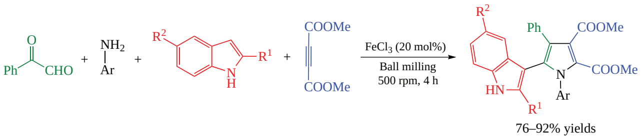
Iron(III) chloride has been found to serve as an efficient catalyst for a mechanochemical (ball milling) one-pot four-component cascade reaction of phenyl glyoxal, anilines, indoles and activated alkyne affording highly-substituted 3-(1*H*-pyrrol-2-yl)-1*H*-indoles. The procedure is beneficial because of mild conditions, easily available starting materials, cheap catalyst and possibility for scaling.



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Nowadays, green chemistry plays an important role for environment. In this context, development of mechanochemical solvent-free ball milling or a grinding approach has attracted considerable interest. Carrying out a reaction under solvent-free conditions at room temperature is an effective approach to eliminate the use of volatile organic compounds and to obtain the greenness in the process.[1–3] Ball milling has been successfully used in polymerization reactions,[4] multicomponent organic syntheses[5] including gaseous reagents,[6] carbon materials[7] and asymmetric organic syntheses.[8]

As one of the most important and well explored nitrogen-containing heterocyclic compounds, pyrroles are present in a wide range of natural products.[9] Functionalized pyrroles play an important role in organic synthesis,[10,11] medicinal chemistry,[12] and materials science.[13] Tri- or tetra-substituted pyrroles act as anti-inflammatory agents[14] and also show antibacterial activity.[15] Pyrrole-fused benzisothiazole skeleton is an organic light-emitting diode material which performs good photoelectric properties,[16] and some random ternary copolymers containing fragments of fused pyrroles show photovoltaic properties.[17] One penta-substituted pyrrole derivative is used as the prescribed antihypercholesterolemic drug Atorvastatin.[9] Generally, the classical directions to synthesize polysubstituted pyrroles rely on the Knorr reaction,[18] the Paal–Knorr cyclization,[19] the Hantzsch reaction,[20,21] and some other methods.[22–24]

On the other hand, indole is known as ‘Lord of the Rings’ of the family of heterocyclic compounds as this moiety is the core structure of a wide range of biologically and pharmaceutically active molecules.[25] Considering the importance of these two classes of compounds, we envisaged that compounds containing both of these two heterocyclic moieties should have a higher biological importance.

In recent years, multicomponent reactions are believed to be efficient since they enable to avoid time consumption and costly purification processes, as well as protection–deprotection steps.[26] The reactions proceeding in a cascade manner are the best to generate complex heterocycles and natural products with several degrees of structural diversity in one pot.[27,28] The use of nonhazardous inexpensive metals, *e.g.*, iron, has attracted interest in organic synthesis to catalyze relevant reactions. Iron-based catalysts have been shown to endorse a broad range of organic transformations, such as cross-couplings, allylations, hydrogenations, and direct C–H bond functionalization.[29,30]

In this communication, we are pleased to report a mechanochemical fast and cascade synthesis of penta-substituted pyrroles in the presence of iron(III) chloride under ball milling conditions at room temperature, the reactants being phenylglyoxal, anilines, indoles and activated alkyne (Scheme 1).[†] To the best of our knowledge, there is no other documented process to explore this multicomponent synthesis by mechanochemical activation within a short reaction time.

For our initial study, we have optimized the reaction conditions by varying different catalysts. Phenylglyoxal **1**, *p*-toluidine **2a**, indole **3a** and dimethyl acetylenedicarboxylate **4** were selected as the model substrates (see Scheme 1). The reaction was conducted under different conditions with variation of catalyst,

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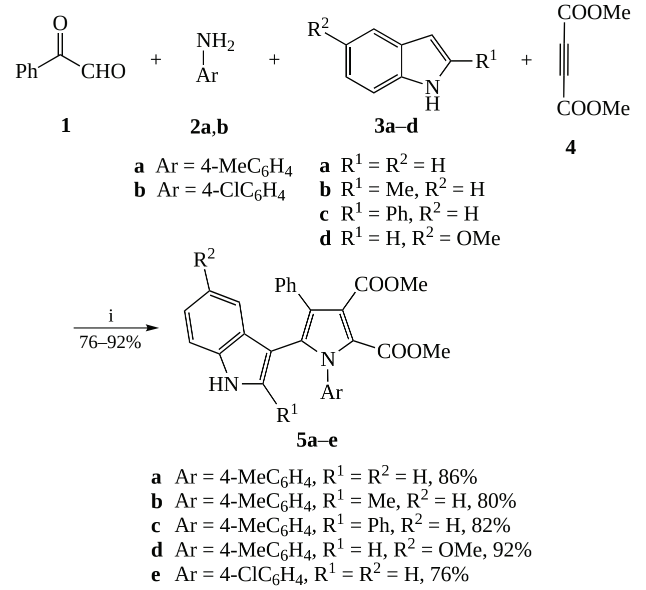
[†] A planetary ball milling apparatus Retsch PM100 was employed using four balls (stainless steel, size 10 mm). The reaction was performed in a 50 ml grinding jar. For each reaction, a mixture of phenyl glyoxal **1** (1 mmol), aniline **2** (1 mmol), indole **3** (1 mmol) and $FeCl_3$ (20 mol%) was ball-milled for 30 min. Then dimethyl acetylenedicarboxylate (**4**, 1 mmol) was added, and the milling was continued for 3.5 h at 500 rpm at room temperature (a 30 min interval). After completion of the reaction (TLC monitoring), the reaction mixture was extracted with ethyl acetate (2 × 15 ml). The organic layer was washed with water (2 × 10 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was subjected to column chromatography using light petroleum–ethyl acetate mixtures as the eluent to obtain the analytically pure product.



1 **2a**,**b** **3a**–**d** **4**

a Ar = 4-MeC_6H_4
b Ar = 4-ClC_6H_4

a $R^1 = R^2 = H$
b $R^1 = Me, R^2 = H$
c $R^1 = Ph, R^2 = H$
d $R^1 = H, R^2 = OMe$

5a–**e**

a Ar = 4-MeC_6H_4, $R^1 = R^2 = H$, 86%
b Ar = 4-MeC_6H_4, $R^1 = Me$, $R^2 = H$, 80%
c Ar = 4-MeC_6H_4, $R^1 = Ph$, $R^2 = H$, 82%
d Ar = 4-MeC_6H_4, $R^1 = H$, $R^2 = OMe$, 92%
e Ar = 4-ClC_6H_4, $R^1 = R^2 = H$, 76%

Scheme 1 *Reagents and conditions*: i, $FeCl_3$ (20 mol%), ball milling (500 rpm), room temperature, 4 h.

Table 1 Optimization of the reaction conditions for model reactants **1**, **2a**, **3a**, and **4**.[a]

Entry	Catalyst	Catalyst loading/mol%	*t*/h	Yield of **5a** (%)[b]
1	–	–	5	0
2	$FeCl_3$	20	4	86
3	$FeBr_3$	20	4	32
4	$Fe(OTf)_3$	20	4	18
5	$AlCl_3$	20	4	ND[c]
6	$BF_3{\cdot}OEt_2$	20	4	ND[c]
7	$FeCl_3$	20	4	87[d]
8	$FeCl_3$	20	6	85
9	$FeCl_3$	30	4	86
10	$FeCl_3$	10	4	54
11	$FeCl_3$	20	4	84[e]

[a] Procedure: a mixture of **1** (1 mmol), **2a** (1 mmol), **3a** (1 mmol) and catalyst was ball milled for 30 min, then **4** (1 mmol) was added, and the milling (500 rpm) was continued for 3.5 h. [b] Isolated yields. [c] ND is not detected by TLC. [d] MeCN (0.2 ml) was used as solvent. [e] In 10 mmol scale.

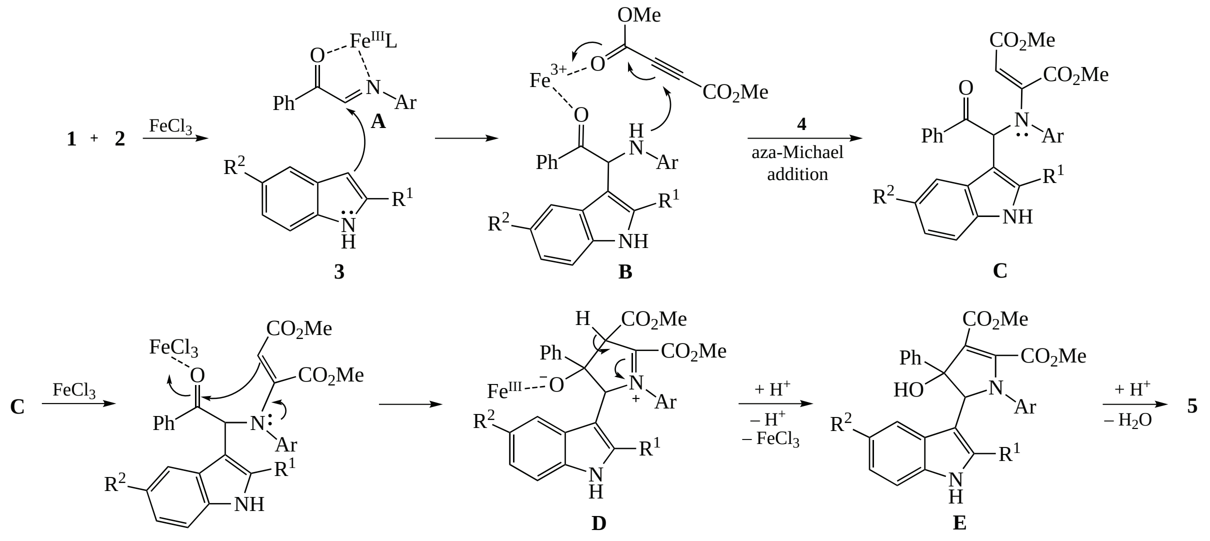
catalyst loading, speed of rotation and time (Table 1). Preliminary optimization experiments indicated that in the absence of any catalyst the reaction did not proceed and the desired product, dimethyl 5-(1*H*-indol-3-yl)-4-phenyl-1-(*p*-tolyl)-1*H*-pyrrole-2,3-dicarboxylate **5a** was not obtained under solvent-free ball milling conditions (entry 1). Based on our previous experiences in iron-catalyzed reactions,[31–34] we used 20 mol% of $FeCl_3$ as the catalyst, so the desired product **5a** was obtained in 86% yield after 4 h of milling at 500 rpm speed (entry 2). Next, we tested some other iron salts, $FeCl_3$ was found to be superior to $FeBr_3$ or $Fe(OTf)_3$ (entries 3, 4). Other common Lewis acids were not effective (entries 5, 6). Although the reactions were carried out as the solvent-free ones, adding very little MeCN (0.2 ml per 1 mmol scale) improved the yield slightly (entry 7). Prolongation of the reaction time did not improve the yield noticeably (entry 8). Catalyst amount of 20 mol% looked optimal, and its increasing was not crucial while its decreasing dropped the yields (entries 9, 10). Finally, the optimized conditions were achieved using 20 mol% $FeCl_3$ under solvent-free conditions for 4 h.

Based on the optimized reaction conditions, we checked the scope of the procedure (see Scheme 1). During optimization we have observed that *p*-toluidine gave the desired product **5a** with excellent yields (86%). Methyl and phenyl-substituted indoles at position 2 reacted smoothly to provide good to excellent yields of products **5b** (80%) and **5c** (82%). 5-Methoxyindole **3d** also gave good result with *p*-toluidine (product **5d**, 92%). In addition, 4-chloroaniline was used to react with other reactants when 76% yield of **5e** was obtained.

All these reactions were performed open to atmosphere, and they were not sensitive to air and moisture. The reaction is highly regioselective as nothing of other regioisomer was formed. All of the known synthesized compounds have been characterized by spectral data while for new compounds spectral and analytical data were obtained. The potential synthetic applicability of this method was investigated on the gram scale using the model reaction, when 3.9 g (84%) of product **5a** was prepared (see Table 1, entry 11).

We have proposed a plausible mechanism for this multicomponent cascade reaction (Scheme 2). Initially, phenylglyoxal **1** and aniline **2** form *C*-acylimine intermediate **A** which undergoes nucleophilic addition by the indole nucleophile **3** (facilitated by the Fe salt)[35] to produce intermediate **B**. Iron-catalyzed aza-Michael addition of amine **B** with activated alkyne **4** gives the Michael adduct **C**,[36] which would further undergo cascade cyclization to produce a cyclic iminium salt **D** in the presence of $FeCl_3$.[37] Deprotonation of iminium intermediate **D** afforded intermediate **E** which gave the final product **5** after removal of water molecule.

In summary, we have developed a solvent-free mechanochemical cascade synthesis of indole-substituted



Scheme 2

pyrrole derivatives in the presence of iron(III) chloride in a short reaction time. The procedure is applicable for the gram-scale synthesis without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of polysubstituted pyrrole derivatives. The present reaction most likely occurs *via* the sequential imine formation/nucleophilic addition/aza-Michael addition/cyclization. Readily available chemicals as starting materials using cheap catalyst, a broad substrate scope, aerobic reaction conditions, and operational simplicity are the notable advantages of the present approach. These advantages render this protocol facile and suitable to create indole-substituted pyrrole derivatives.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.018.

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