Iron Salt-cataltzed Multipoint Alkylation of Pyrrole with Vinyl Ketones

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(Received April 4, 2008; CL-080346; E-mail: titoh@chem.tottori-u.ac.jp)

Pyrrole reacted with vinyl ketones in the presence of 3 mol % of iron(II) tetrafluoroborate or alumina-supported iron(III) perchlorate to give multipoint-alkylated products in good yield. Most notably, 4,5-dialkylated 2-acetylpyrrole was obtained in good yield when 2-acetylpyrrole was allowed to react with an excess amount of vinyl ketones.

Iron is one of the most abundant and environmentally friendly metals on the earth and various types of iron metal-catalyzed organic transformations have been reported during the past decades.[1] We have also been fascinated by the possibility of iron-catalyzed reactions and have developed several of them: the intramolecular cyclization of cyclopropanedithioacetals,[2] the [2 + 2]-cycloaddition of *trans*-anethol,[3] the [2 + 3]-type cycloaddition of styrene derivatives to 1,4-benzoquinone,[4] the 1,4-addition of β-ketoesters to vinylketones,[5] and the enantioselective Michael addition of thiols to α,β-unsaturated carbonyl compounds.[6] We then recently established the iron salt-catalyzed Friedel–Crafts type alkylation of indoles[7] and the Nazarov type cyclization of thiophene.[8] During the course of such studies, we further found that alkylation of pyrrole (**1**) with 3-buten-2-one (**2a**) took place using iron(II) tetrafluoroborate as catalyst and that the alkylated products **3**, **4**, and **5** were produced, though their chemical yields were poor.[9] On the other hand, only a polymerized product was obtained if the reaction was carried out in the presence of iron(III) chloride (Figure 1). Although the pyrrole moiety is very common in many biologically active or functional molecules, no such simple alkylation protocol was reported when we undertook the present work.[9,10] Here, we wish to report the results of optimization of our iron salt-catalyzed multipoint alkylation of pyrrole.[11]

We initially attempted to optimize the reaction conditions using pyrrole (**1**) as a substrate; unfortunately, it was unsuccessful in improving the chemical efficiency of the alkylation product due to side reactions. It was found, however, that alkylation of 2-acetylpyrrole (**6**) with 3-buten-2-one (**2a**) proceeded smoothly and double alkylation product **8a** was obtained in acceptable yield (Entry 1, Table 1).[12]

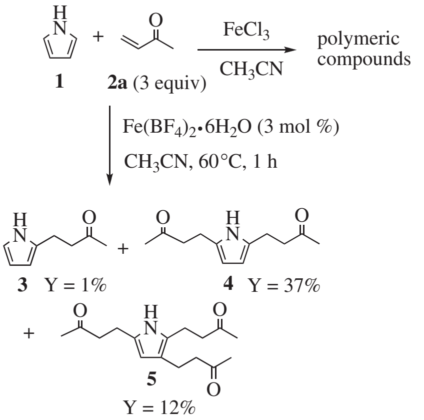
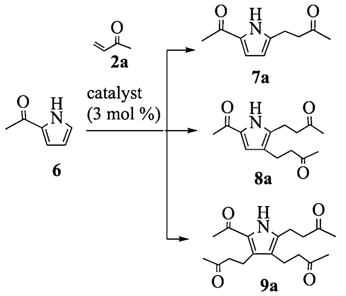


Figure 1. Iron salt-catalyzed alkylation of pyrrole.



(1)

Therefore, we decided to optimize the reaction conditions using 2-acetylpyrrole (**6**) as a substrate. The reaction was carried out as follows: to a solution of **6** (109 mg, 1.0 mmol) and **2a** (210 mg, 3.0 equiv) in acetonitrile (CH_3CN) (1.0 mL) was added $Fe(BF_4)_2 \cdot 6H_2O$ (16 mg, 3 mol %) and the mixture was stirred at 60 °C for 24 h. After being cooled to rt, the mixture was diluted with ethyl acetate. The organic layer was filtered through a florisil short column and evaporated to dryness, and subsequent purification using silica gel thin layer chromatography (TLC) afforded the product **8a** (172 mg) in 69% yield (Entry 1, Table 1). Very simple alkylation of pyrrole was thus accomplish-

Table 1. Results of iron salt-mediated reaction of 2-acetylpyrrole (**6**) with 3-buten-2-one (**2a**)

Entry	Solvnet	Catalyst[a]	Temp /°C	Time /h	Yield/%[b] **7a**	**8a**	**9a**	Recovery of **6**/%
1	CH_3CN	$Fe(BF_4)_2 \cdot 6H_2O$	60	24	0	69	0	25
2	CH_3CN	$Fe(BF_4)_2 \cdot 6H_2O$	rt	168	0	**72**	0	6
3	CH_3CN	$FeCl_2$	60	24	6	36	2	42
4	CH_3CN	$Fe(NO_3)_3$	60	24	6	4	0	84
5	CH_3CN	$Fe_2(SO_4)_3$	60	24	5	36	0	42
6	CH_3CN	$FeCl_3 \cdot 6H_2O$	60	24	7	54	0	<30[c]
7	CH_3CN	$K_3Fe(CN)_6$	60	24	0	0	0	94
8	CH_3CN	Fe_3O_4 (II:III = 1:2)	60	24	0	0	0	83
9	CH_3CN	FeO(OH)	60	24	0	0	0	98
10	CH_3CN	$Fe(ClO_4)_3 \cdot nH_2O$	60	24	3	66	3	18
11	CH_3CN	$Fe(ClO_4)_3–Al_2O_3$	60	24	1	65	24	0
12	CH_3CN	$Fe(ClO_4)_3–Al_2O_3$	rt	168	0	70	6	6
13	neat	$Fe(ClO_4)_3–Al_2O_3$	60	24	0	**80**	**13**	0
14	CH_2Cl_2	$Fe(ClO_4)_3–Al_2O_3$	60	24	0	73	9	0
15	Hexane	$Fe(ClO_4)_3–Al_2O_3$	60	24	0	70	13	0
16	MeOH	$Fe(ClO_4)_3–Al_2O_3$	60	24	18	25	0	52
17	H_2O	$Fe(ClO_4)_3–Al_2O_3$	60	24	0	0	0	94
18	CH_3CN	$Fe(ClO_4)_3–Al_2O_3$ + TEMPO[d]	60	24	0	0	0	90
19	CH_3CN	$Fe(ClO_4)_3–Al_2O_3$ + BHT[e]	60	24	0	72	13	0
20	CH_3CN	$Fe(ClO_4)_3–Al_2O_3$ + 2,6-lutidine[f]	60	24	0	0	0	94

[a] 3 mol % vs. pyrrole. [b] Isolated yield. [c] Due to formation of a large amount of polymeric product, isolation of **6** from the reaction mixture was unsuccessful. [d] 1.0 equiv (vs. pyrrole) of TEMPO was added. [e] 1.0 equiv (vs. pyrrole) of BHT was added. [f] 1.0 equiv (vs. pyrrole) of 2,6-lutidine was added.

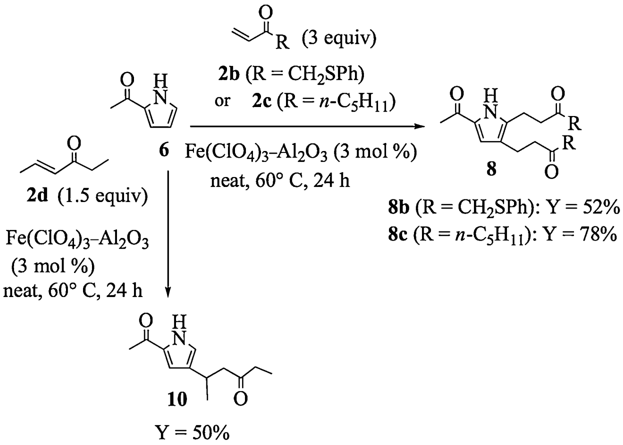
ed. Chemical yield of **8a** was slightly improved up to 72% when the reaction was carried out at rt, though the starting compound **6** was not consumed and was recovered it in 6% yield after 168 h of reaction at rt (Entry 2). We anticipated that the real catalyst may be iron(III) species derived from $Fe(BF_4)_2 \cdot 6H_2O$ by the aerobic oxidation during performance of the reaction process.[5]

Strong Lewis acids, $Fe(NO_3)_3$, $Fe_2(SO_4)_3$, and $FeCl_3$, catalyzed the alkylation of **6**, but the results were not satisfactory (Entires 4–6). The catalytic activity was significantly dependent on the anionic part of the iron(III) salts: $K_3Fe(CN)_6$, Fe_3O_4, and FeO(OH) showed no catalytic activity (Entries 7–9). To our delight, the desired alkylation product was obtained when iron(III) perchlorate [$Fe(ClO_4)_3$] was used as a catalyst and, in particular, alumina-supported iron(III) perchlorate [$Fe(ClO_4)_3$–Al_2O_3][3] afforded dialkylated pyrrole **8a** and trialkylated pyrrole **9a** in 65% and 24% yields, respectively (Entries 11).

Choice of the solvent is very important: the reaction proceeded smoothly in CH_3CN, hexane, or CH_2Cl_2, while desired product **8a** was obtained in poor yield when the reaction was conducted in MeOH (Entry 16), and no reaction took place in H_2O (Entry 17). Monoalkylated product **7a**[13] was also obtained in 18% yield when the reaction was carried out in MeOH (Entry 16). The best yield of **8a** (80%) was recorded when the reaction was carried out without solvent at 60 °C (Entry 13). These results were completely different from those of iron salt-catalyzed alkylation of indole that we previously reported; alkylation product was obtained in good yield in MeOH or H_2O when indole was subjected to the reaction with **2a** using $Fe(ClO_4)_3$–Al_2O_3 or $Fe(BF_4)_2 \cdot 6H_2O$ as catalyst.[7] We previously demonstrated that an ionic liquid solvent such as [bmim][TFSI] gave better results than those in CH_3CN solvent for the alkylation of indole.[7] Although alkylation of pyrrole **6** also proceeded very smoothly in the [bmim][TFSI] solvent system, unfortunately, it was quite difficult to extract product **8a** from the ionic liquid solution.

The reaction was completely inhibited by addition of 1.0 equiv of TEMPO (Entry 18). On the contrary, no inhibition was observed when 1.0 equiv (vs. pyrrole **6**) of 1,6-di-*t*-butylphenol (BHT) was added to the reaction (Entry 19). It was also found that the reaction was completely inhibited by addition of a base: no reaction took place when the reaction was conducted in the presence of 1.0 equiv of 2,6-lutidine (Entry 20). From these results, we are assuming that the mild Lewis acid property of iron salt might contribute to the present iron salt-catalyzed alkylation of pyrrole.

The reaction conditions having thus been optimized, we next demonstrated alkylation of 2-acetylpyrrole with three types of vinyl ketones, **2b**, **2c**, and **2d** (Scheme 1). 3,4-Dialkylated pyrrole **8b** was obtained in 52% yield when vinyl ketone **2b** reacted with **6**. To our delight, dialkylated product **8c** was obtained in better yield (78%) for the reaction of **2c** (Scheme 1, right).[12] On the other hand, interesting regiospecific alkylation was recorded when 1.5 equiv of **2d** was used as an acceptor (Scheme 1, left): the only product obtained was a monoalkylated compound and 4-alkylated pyrrole derivative **10** was obtained as the sole product in 50% yield.[12] Because no reaction took place when 4-methylpent-3-en-2-one was allowed to react with pyrrole **6**, we are assuming that the result of present alkylation was significantly influenced by the steric bulkiness of the reaction center.



Scheme 1.

In summary, we demonstrated the very simple alkylation of pyrrole derivatives with vinyl ketone in the presence of two types of iron salts; $Fe(BF_4)_2 \cdot 6H_2O$ and $Fe(ClO_4)_3$–Al_2O_3 worked as efficient catalysts to give dialkylation products. The results looked very similar to those of the reaction of indole which we previously reported. However, details of the reaction profile were different from that of alkylation of indole,[7] because alkylation of indole with vinyl ketone took place in water while no reaction occurred with pyrrole. Although the reaction mechanism is still unclear, the alkylation products were obtained in moderate to good yield under very mild reaction conditions: the reaction proceeds very smoothly at rt or 60 °C and requires no tedious argon atmospheric conditions. Further investigation of the scope and limitations of this iron salt-catalyzed reaction will make it even more valuable.

This work was supported by a Grant-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Published on the web (Advance View) June 21, 2008; doi:10.1246/cl.2008.794