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HAFNIUM CHLORIDE CATALYZED CONJUGATE ADDITION OF PYRROLE, PYRAZOLE AND IMIDAZOLE TO α,β-UNSATURATED KETONES

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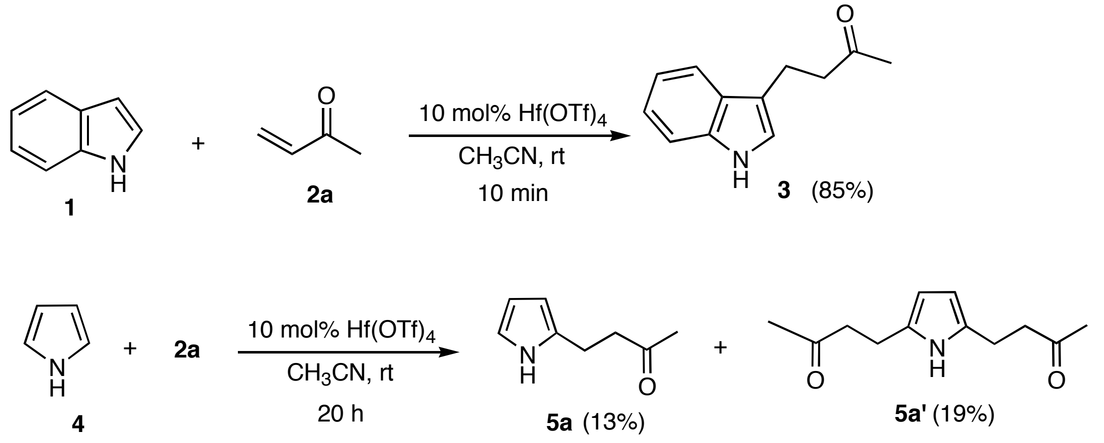
Abstract – Pyrrole, pyrazole and imidazole undergo conjugate addition with α,β-unsaturated ketones in the presence of a catalytic amount of hafnium chloride at room temperature. Although the reaction of pyrrole gave 2,5-substituted *C*-adduct mainly, those of pyrazole and imidazole gave the corresponding *N*-adducts in excellent yields.

INTRODUCTION

Conjugate addition is an important reaction in organic synthesis. In general, an addition of nucleophiles to α,β–unsaturated carbonyl compounds requires basic or acidic conditions. So far, acid–catalyzed conjugate additions of pyrroles to enones have been reported, in which $Cu(OTf)_2$,[1] $InCl_3$,[2] benzyl imidazolidinone-HX salts,[3] montmorillonite K10,[4] silica gel supported $BiCl_3$,[5] and aluminum dodecyl sulfate[6] have been employed as useful catalysts for the reactions. However such acid catalyzed reactions of pyrrole are limited and require careful control of acidity to prevent polymerization. On the other hand, there are some reports of conjugate additions for pyrazoles,[7] and imidazoles[8] to enones. We are interested in a Lewis acidity and a reactivity of HfX_4[9] and have reported that hafnium trifluoromethanesulfonate [$Hf(OTf)_4$] is found to be an effective catalyst for conjugate addition of indoles to enones.[10] In this paper, we report an extension study of the Hf-catalyzed 1,4-addition reaction of 5-membered nitrogen heterocycles, such as pyrrole, pyrazole, and imidazole to enones.

RESULTS AND DISCUSSION

We have recently reported 1,4-addition reaction of indole (**1**) to methyl vinyl ketone (**2a**) in the presence of 10 mol% $Hf(OTf)_4$ in CH_3CN. The reaction proceeded well in a short time to give 4-(3-indolyl)butan-2-one (**3**) in 85% yield.[10] First, this addition reaction of pyrrole (**4**) with **2a** was examined under the same reaction conditions. However, the reaction was not clean and gave a mixture of 2-(2-oxo-4-butanyl)pyrrole (**5a**)[4] and 2,5-bis(2-oxo-4-butanyl)pyrrole (**5a’**)[4] in 13% and 19% yields, respectively, as shown in Scheme 1.



Scheme 1

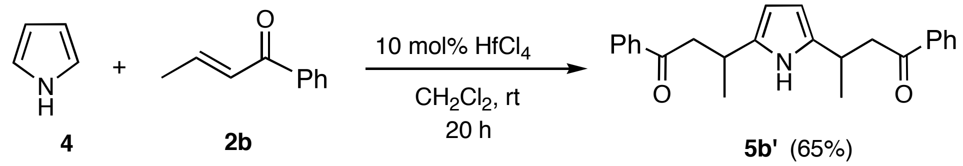
When CH_2Cl_2 was used instead of CH_3CN, the chemical yields of **5a** and **5a’** were increased to be 27% and 34% yields. When $Hf(OTf)_4$ was changed to $HfBr_4$ or $HfCl_4$, **5a’** was formed selectively or preferentially. The use of $ScCl_3$ took longer period of reaction time and gave a similar result to those of $HfBr_4$ and $HfCl_4$. On the other hand, $InCl_3$ gave a mixture of **5a** and **5a’**.[11] For the formation of **5a’**, CH_2Cl_2 was found to be a better solvent than other solvents such as CH_3CN, toluene or THF. These results are shown in Table 1. The preferable formation of **5a’** indicates the second addition of **4** to **5a** is faster than that of the initial addition to **2a** under the conditions.

Table 1. Catalytic activity of metal salts in the reaction of pyrrole (**4**) with methyl vinyl ketone (**2a**).

Entry	Catalyst[a]	Solvent	Time (h)	Yield(%)[b,c]	
				5a	**5a'**
1	$Hf(OTf)_4$	CH_2Cl_2	5	27	34
2	$HfBr_4$	CH_2Cl_2	5	0	43
3	$HfCl_4$	CH_2Cl_2	5	6	63
4	$ScCl_3$	CH_2Cl_2	20	7	48
5	$InCl_3$	CH_2Cl_2	5	22	20
6	$HfCl_4$	CH_3CN	5	7	43
7	$HfCl_4$	toluene	5	7	43
8	$HfCl_4$	THF	5	7	53

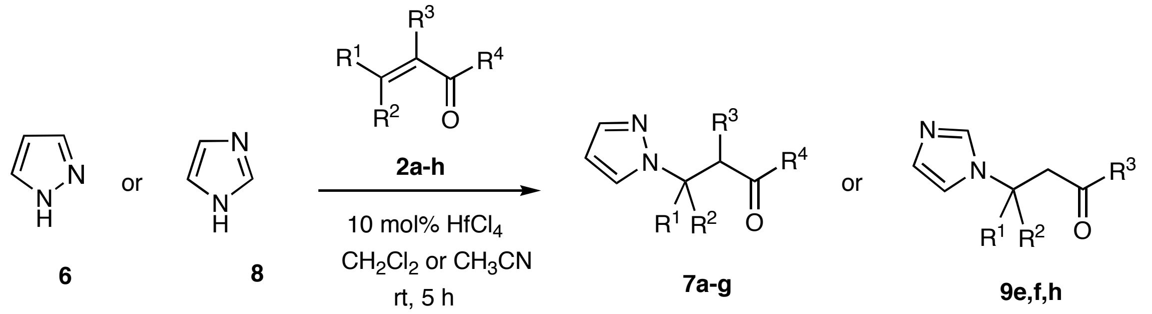
[a] 10 mol% of catalyst was used at room temperature. [b] Isolated yield after the purification by silica gel column chlomatography. [c] A dimmer of methyl vinyl ketone was produced as a majour by-product.

The conjugate addition reaction of **4** to phenyl 1-propenyl ketone (**2b**) also took place and gave only 2,5-bis(1-phenyl-1-butanon-3-yl)pyrrole (**5b'**) in 65% yield.



Scheme 2

Conjugate additions of pyrazole (**6**)[7] and imidazole (**8**)[8a-e] to **2a** required harsh or specific conditions, e.g. refluxing for 4 days without solvent,[7,8a] refluxing for 24 h in dioxane,[8b] solvent free conditions in the presence of Bi(NO)$_3$,[8c] Al$_2$O$_3$ supported CeCl$_3$/NaI reagent without solvent,[8d] or aluminum dodecyl sulfate.[8e] In all cases, the additions of **6** and **8** occurred not at the carbon center but at the nitrogen center on pyrazole and imidazole rings. We have examined their reactions with various acyclic and cyclic α,β-unsaturated ketones in the presence of 10 mol% HfCl$_4$ at room temperature for 5 h, as shown in Scheme 3. These results are listed in Table 2. The reaction of **6** with **2a** took place at room temperature for 5 h to give 4-(*N*-pyrazoyl)butan-2-one (**7a**) in 72% yield. The reactions of **6** with other acyclic enones and enals such as **2b**, **2c**, and **2d** gave **7b**, **7c** and **7d** in excellent yields (entries 2-4).



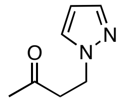
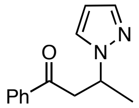
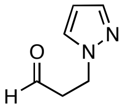
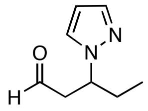
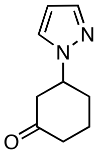
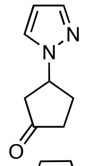
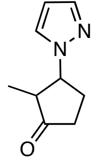
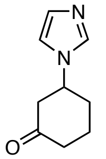
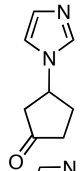
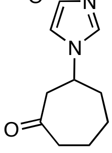
a; $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
b; $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = Ph$
c; $R^1 = R^2 = R^3 = R^4 = H$
d; $R^1 = Et$, $R^2 = R^3 = R^4 = H$
e; $R^1 = R^3 = H$, $R^2 = R^4 = (CH_2)_3$
f; $R^1 = R^3 = H$, $R^2 = R^4 = (CH_2)_2$
g; $R^1 = H$, $R^3 = CH_3$, $R^2 = R^4 = (CH_2)_2$
h; $R^1 = R^3 = H$, $R^2 = R^4 = (CH_2)_4$

Scheme 3

The reactions with cyclic enones (**2e** and **2f**) proceeded well to give the corresponding *N*-pyrazoyl cyclic ketones (**7e** and **7f**) in 90% and 97% yields, respectively (entries 5 and 6). While that with 2-methylcyclopentenone (**2g**) gave **7g** in 42% yield for 5 h but the yield was increased to be 73% after 15

h. On the other hand, the $HfCl_4$ catalyzed conjugate addition of **8** with acyclic enones did not occur but with cyclic enones (**2e**, **2f** and **2h**) occur to give 3-(*N*-imidazolyl)cycloalkanones (**9e**, **9f** and **9h**) (entries 8-10). For these reactions of imidazole, the use of CH_3CN gave higher yield than that of CH_2Cl_2. Somehow the chemical yield of **9f** did not increase over 34%.

Table 2. $HfCl_4$-Catalyzed 1,4-addition of **6** and **8** to enones (**2a**-**2h**)[a]

Entry	Nucleophile	Enone	Product		Yield(%)[b]
1	**6**	**2a**		**7a**	72
2	**6**	**2b**		**7b**	94
3	**6**	**2c**		**7c**	94
4	**6**	**2d**		**7d**	72
5	**6**	**2e**		**7e**	90
6	**6**	**2f**		**7f**	97
7	**6**	**2g**		**7g**	42[c]
8	**8**	**2e**		**9e**	63[d]
9	**8**	**2f**		**9f**	25[c,d]
10	**8**	**2h**		**9h**	70[d]

[a] All reactions were carried out at r.t. for 5 h in CH_2Cl_2. [b] Isolated yield after purification by silica gel column chromatography. [c] The reactions for 15 h gave **7g** in 73% yield and **9f** in 34% yield. [d] CH_3CN was used as a solvent.

In summary, we have revealed that $HfCl_4$ is an effective catalyst for conjugate addition of 5-membered nitrogen heterocycles to α,β-enones. The conjugate addition reaction of pyrrole occurs at C-2 and C-5 positions. While in the case of pyrazole and imidazole, the addition occurs at nitrogen on the rings to give β-*N*-substituted carbonyl compounds.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-AL-300 (300 MHz and 75 MHz) spectrometer in $CDCl_3$ with tetramethylsilane internal standard or $CDCl_3$. MS spectra were obtained on JMS-GC mate. IR spectra were recorded on JASCO FT/IR-410 instrument. Thin layer chromatography (TLC) was performed with Merck $60F_{245}$ precoated silica gel plates. Column chromatography was carried out using Merck silica gel 60 (70-230 mesh) for gravity column.

General Procedure

A mixture of pyrrole (1 mmol), pyrazole or imidazole, enone (**2**) (2.4 mmol), and $HfCl_4$ (32 mg, 10 mol%) in CH_2Cl_2 (5 mL) or CH_3CN was stirred at room temperature for 5 h. Then, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$ for 3 times. The combined organic layers were washed with water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel to afford the addition product.

4-(1*H*-Indol-3-yl)butan-2-one (3).[12] White powder; *Rf* = 0.13 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.84 (2H, t, J = 7.4 Hz), 3.05 (2H, t, J = 7.4 Hz), 6.98 (1H, d, J = 2.4 Hz), 7.11 (1H, td, J = 7.9, 1.3 Hz), 7.19 (1H, td, J = 7.9, 1.3 Hz), 7.34 (1H, d, J = 7.9 Hz), 7.58 (1H, d, J = 7.9 Hz), 7.94 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 30.3, 44.0, 111.1, 115.1, 118.6, 119.2, 121.4, 121.9, 127.1, 136.3, 208.8.

4-(1*H*-Pyrrol-2-yl)-butan-2-one (5a).[4] Colorless oil; *Rf* = 0.15 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, s), 2.77-2.83 (4H, m), 5.86 (1H, s), 6.06 (1H, d, J =2.6 Hz), 6.63 (1H, d, J =2.6 Hz), 8.46 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 30.1, 44.2, 105.3, 107.8, 116.7, 136.6, 209.6.

4-{5-[4-(2-Oxo-butyl)]-1*H*-pyrrol-2-yl}-butan-2-one (5a').[4] Colorless oil; *Rf* = 0.38 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (6H, s,), 2.71-2.81 (8H, m), 5.69 (2H, d, J =2.6 Hz), 8.43 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (2C), 30.0 (2C), 44.0 (2C), 104.8 (2C), 130.4 (2C), 209.1 (2C).

2,5-Bis(1-phenyl-1-butanon-3-yl)pyrrole (5b'). Colorless oil; *Rf* = 0.15 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, d, J =7.0 Hz), 1.28 (3H, d, J =7.0 Hz), 3.01-3.24 (4H, m), 3.43 (2H, quint, J =7.0 Hz), 5.74 (2H, d, J =2.6 Hz), 7.29-7.49 (6H, m), 7.78-7.87 (4H, m), 8.67 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 20.0, 27.8, 27.9, 47.1, 47.2, 102.6, 102.7, 128.1 (4C), 128.5 (2C), 128.6

(2C), 133.0, 133.1, 135.6 (2C), 137.1 (2C), 200.2 (2C); IR (neat) 1683, 3376 cm^{-1}; MS (EI) *m/z* 359 (M$^+$); HRMS (EI) *m/z* Calcd for $C_{24}H_{25}NO_2$: 359.1885 (M$^+$), Found: 359.1887.

4-(Pyrazol-1-yl)butan-2-one (7a).[8a] Yellow oil; *Rf* = 0.35 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, s), 3.05 (2H, t, *J* =6.4 Hz), 4.39 (2H, t, *J* =6.4 Hz), 6.20 (1H, t, *J* =2.2 Hz), 7.42 (1H, d, *J* =2.2 Hz), 7.48 (1H, d, *J* =2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 26.1, 32.2, 106.6, 126.5, 138.8, 207.9.

1-Phenyl-3-(pyrazol-1-yl)butan-1-one (7b). Colorless oil; *Rf* = 0.30 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (3H, d, *J* =6.8 Hz), 3.32 (1H, dd, *J* =17.4, 6.8 Hz), 3.79 (1H, dd, *J* =17.4, 6.8 Hz), 5.06 (1H, sixtet, *J* =6.8 Hz), 6.18 (1H, t, *J* =2.0 Hz), 7.40-7.57 (5H, m), 7.90-7.93 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 45.3, 53.6, 104.8, 128.1 (2C), 128.6 (2C), 133.4 (2C), 136.7, 139.4, 197.4; IR (neat) 1683 cm^{-1}; MS (EI) *m/z* 214 (M$^+$); HRMS (EI) *m/z* Calcd for $C_{13}H_{14}N_2O$: 214.1106 (M$^+$), Found: 214.1110.

3-(Pyrazol-1-yl)propionaldehyde (7c).[7] Colorless oil; *Rf* = 0.25 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (2H, t, *J* =6.2 Hz), 4.43 (2H, t, *J* =6.2 Hz), 6.19 (1H, s), 7.41 (1H, d, *J* =2.2 Hz), 7.46 (1H, s), 9.78 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 44.8, 105.5, 129.8, 139.7, 199.3.

3-(Pyrazol-1-yl)pentanal (7d). Colorless oil; *Rf* = 0.50 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (3H, t, *J* =7.7 Hz), 1.68-1.81 (1H, m), 1.84-1.99 (1H, m), 2.81 (1H, ddd, *J* =17.6, 4.8, 1.1 Hz), 3.16 (1H, ddd, *J* =17.6, 8.4, 1.1 Hz), 4.53 (1H, seventet, *J* =4.8 Hz), 6.13 (1H, t, *J* =2.2 Hz), 7.36 (1H, d, *J* =2.2 Hz), 7.45 (1H, s), 9.61 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 28.5, 48.6, 58.2, 104.8, 129.4, 139.6, 199.5; IR (neat) 1715, 2551 cm^{-1}; MS (EI) *m/z* 152 (M$^+$); HRMS (EI) *m/z* Calcd for $C_8H_{12}N_2O$: 152.0950 (M$^+$), Found: 152.0948.

3-(Pyrazol-1-yl)cyclohexanone (7e). Colorless oil; *Rf* = 0.50 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66-1.81 (1H, s), 2.01-2.12 (1H, m), 2.22-2.29 (2H, m), 2.41-2.46 (2H, m), 2.82 (1H, dd, *J* =14.5, 5.0 Hz), 2.99 (1H, dd, *J* =14.5, 10.0 Hz), 4.50-4.60 (1H, m), 6.25 (1H, t, *J* =2.2 Hz), 7.41 (1H, d, *J* =2.2 Hz), 7.54 (1H, d, *J* =2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 31.8, 40.6, 47.7, 69.75, 105.3, 127.5, 139.4, 207.9; IR (neat) 1714 cm^{-1}; MS (EI) *m/z* 164 (M$^+$); HRMS (EI) *m/z* Calcd for $C_9H_{12}N_2O$: 164.0950 (M$^+$), Found: 164.0947.

3-(Pyrazol-1-yl)cyclopentanone (7f). Colorless oil; *Rf* = 0.40 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23-2.85 (5H, m), 2.76 (1H, dd, *J* =9.5, 7.7 Hz), 4.94 (1H, quint, *J* =6.6 Hz), 6.24 (1H, t, *J* =2.6 Hz), 7.41 (1H, d, *J* =2.6 Hz), 7.51 (1H, d, *J* =2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 30.3, 36.8, 44.8, 58.6, 105.7, 127.9, 139.7, 215.0; IR (neat) 1746 cm^{-1}; MS (EI) *m/z* 150 (M$^+$); HRMS (EI) *m/z* Calcd for $C_8H_{10}N_2O$: 150.0793 (M$^+$), Found: 150.0798.

2-Methyl-3-(pyrazol-1-yl)cyclopentanone (7g). Colorless oil; *Rf* = 0.50 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* =7.0 Hz), 2.20-2.48 (3H, m), 2.60-6.84 (2H, m), 4.33 (1H, td, *J*

=10.5, 7.7 Hz), 6.26 (1H, t, *J* =2.0 Hz), 7.45 (1H, d, *J* =2.0 Hz), 7.55 (1H, d, *J* =2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 27.8, 36.5, 50.2, 66.1, 105.4, 128.4, 139.8, 215.6; IR (neat) 1746m^{-1}; MS (EI) *m/z* 164 (M^+); HRMS (EI) *m/z* Calcd for $C_9H_{12}N_2O$: 164.0950 (M^+), Found: 164.0946.

3-(Imidazol-1-yl)cyclohexanone (9e).[8c] Colorless oil; *Rf* = 0.29 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67-1.79 (1H, m), 1.98-2.13 (2H, m), 2.27-2.47 (3H, m), 2.68 (1H, dd, *J* =13.9, 11.0 Hz), 2.80 (1H, ddt, *J* =13.9, 4.8, 1.5 Hz), 4.30-4.39 (1H, m), 7.04 (1H, s), 7.24 (1H, s), 7.51 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 32.4, 40.4, 48.7, 55.5, 116.7, 129.7, 135.2, 206.7.

3-(Imidazol-1-yl)cyclopentanone (9f). Colorless oil; *Rf* = 0.27 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22-2.62 (5H, m), 2.83 (1H, dd, *J* =18.4, 8.1 Hz), 4.78 (1H, quint, *J* =8.1 Hz), 7.08 (1H, s), 7.24 (1H, s), 7.55 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6, 37.0, 45.2, 54.2, 116.8, 130.1, 135.6, 212.9; IR (neat) 1746 cm^{-1}; MS (EI) *m/z* 150 (M^+); HRMS (EI) *m/z* Calcd for $C_8H_{10}N_2O$: 150.0793 (M^+), Found: 150.0798.

3-(Imidazol-1-yl)cycloheptanone (9h). Colorless oil; *Rf* = 0.25 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49-1.57 (1H, m), 1.67-1.79 (1H, m), 1.93-2.05 (3H, m), 2.23-2.27 (1H, m), 2.49 (1H, ddd, *J* =15.8, 11.4, 4.4 Hz), 2.57-2.64 (1H, m), 2.81 (1H, dt, *J* =13.9, 2.6 Hz), 3.12 (1H, dd, *J* =13.9, 11.4 Hz), 4.28 (1H, tt, *J* =11.4, 2.9 Hz), 6.91 (1H, s), 7.04 (1H, s), 7.51 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 26.6, 38.8, 43.9, 51.1, 54.8, 116.6, 129.8, 135.2, 209.2; IR (neat) 1702 cm^{-1}; MS (EI) *m/z* 178 (M^+); HRMS (EI) *m/z* Calcd for $C_{10}H_{14}N_2O$: 178.1106 (M^+), Found: 178.1109.

REFERENCES

1. C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia, and A. Linden, *J. Am. Chem. Soc.*, 2005, **127**, 4154.
2. J. S. Yadav, S. Abraham, B. V. Subba Reddy, and G. Sabitha, *Tetrahedron Lett.*, 2001, **42**, 8063.
3. N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370.
4. M. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jimenez, J. C. Palacios, and M. A. Silva, *Green Chem.*, 2001, **3**, 26.
5. Z.-P. Zhan, W.-Z. Yang, and R.-F. Yang, *Synlett*, 2005, 2425.
6. H. Firouzabadi, N. Iranpoor, and F. Nowrouzi, *Chem. Commun.*, 2005, 789.
7. (a) H. Reimlinger and J. F. M. Oth, *Chem. Ber.,* 1964, **97***,* 331.
8. (a) R. Ferroni, L. Milani, D. Simoni, P. Orlandini, M. Guarneri, D. Franze, and A. Bardi, *Farmaco,* 1989, 44, 495. (b) P. M. Weintraub, P. L. Tiernan, and J. C. Huffman, *J. Heterocycl. Chem.*, 1987, **24**, 561. (c) N. Srivastava and B. K. Banik, *J. Org. Chem.*, 2003, **68**, 2109. (d) G. Bartoli, M. Bartolacci, A. Giuliani, E. Marcantoni, M. Massaccesi, and E. Torregiani, *J. Org. Chem.*, 2005, **70**, 169. (e) H. Firouzabadi, N. Iranpoor, and A. A. Jafari, *Adv. Synth. Catal.* 2005, **347**, 655.

9. Reviews; (a) K. Suzuki, ‘Lewis Acid Reagents: Hf-Centered Lewis Acid in Organic Synthesis,’ ed. by H. Yamamoto, Oxford University Press, Int., Oxford, 1999, pp. 177-184. (b) K. Suzuki and S. Yamanori, ‘Lewis Acids in Organic Synthesis: Hf-Centered Lewis Acid in Organic Chemistry,’ Vol. 2, ed. by H. Yamamoto, Wiley-VCH Press, Int., Weinheim, 2000, pp. 849-864.

10. M. Kawatsura, S. Aburatani, and J. Uenishi, *Synlett*, 2005, 2492.

11. According to the reference 2, $InCl_3$ catalyzed reaction of pyrrole gave mono 2-alkylated pyrrole, selectively. However, the results were not reproducible at least by our hands.

12. P. Harrington and M. A. Kerr, *Can. J. Chem.*, 1998, **76**, 1256.