AN EXPERIMENTAL AND THEORETICAL STUDY ON IMIDAZOLIUM-BASED IONIC LIQUID PROMOTED CHLOROMETHYLATION OF AROMATIC HYDROCARBONS

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ABSTRACT

The chloromethylation of aromatic hydrocarbons proceeded efficiently using the reusable imidazolium-based ionic liquid as promoter. Mild reaction conditions, enhanced rates, improved yields, recyclability of ionic liquids, and reagents' reactivity which is different from that in conventional organic solvents are the remarkable features observed in ionic liquids. The ionic liquids were recycled in three subsequent runs with no decrease in activity. In addition, the results of calculations with the Gaussian 98 suite of program are in good accordance with the experimental outcomes.
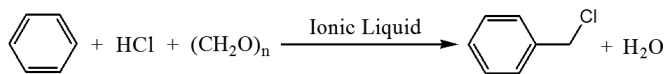
Keywords: Ionic liquid, Chloromethylation, Aromatic hydrocarbons, DFT, Solvent effects

1. INTRODUCTION

Chloromethyl substituted aromatic hydrocarbons are promising key intermediates because of easy transformation to many chemicals such as fine-chemicals, pharmaceuticals, and polymers. The chloromethylation of aromatic hydrocarbons has been documented in previous papers. [1-7] The reaction of aromatic hydrocarbons with hydrochloric acid and trioxane or paraformaldehyde as a formaldehyde precursor sometimes gave chloromethylated products without catalyst. [6-7] however, the rate is slow and insufficient for practical chemical process.

Lewis acids such as zinc chloride, stannic chloride, and boron trifluoride are well-known catalysts for the reaction; among these acids, zinc chloride is an effective catalyst in hydrochloric acid solution. [1-2] however, a stoichiometric amount of catalyst to substrate is required, making the work up procedure tedious. These catalysts, in general, suffer from the inherent problems of corrosiveness, high susceptibility to water, difficulty in catalyst recovery environmental hazards, waste control after the reaction, *etc*. So it is important to replace these highly corrosive, hazards and polluting acid catalysts with environmentally conscious catalysts which are active under mild conditions, and can be easily recovered after the reaction and reused for new reaction. [8] Yoshihiro Sugi *et al.* reported rare-earth metal triflates are active catalysts for this reaction, [9] but the rare-earth metal triflates is expensive, so these catalysts are not suitable to industry.

Ionic liquids (ILs) are very attractive solvents because they have very low vapor pressure and are stable in a wide temperature range.[10-11] Examples of their application in both reactions[12] and separations[13] have been demonstrated. Recently ILs are attracting more attention for the reason that they are showing significant role in controlling the reaction as catalyst. [14] A variety of ILs are successfully applied in many types of reactions such as Friedel-Crafts acylations[15], Alklations[16]. Recently, we reported that IL 1-ethyl-3-methylimidazolium tetrafluoroborate [emim]BF_4 is highly active for the chloromethylation of many aromatic hydrocarbons at 70 ºC and the reaction with 0.3 equiv of the catalyst was completed in 5h with good yields and easy workup.[17] So other imidazolium-based ILs were applied in the chloromethylation of many aromatic hydrocarbons in the paper (**Scheme 1**). Furthermore, study on the experimental results of the aromatic hydrocarbons' chloromethylation with calculations by the Gaussian 98 suite of program was developed for the first time.

Scheme 1: The chloromethylation of aromatic hydrocarbons.

2. EXPERIMENTAL

2.1 Materials

Ionic liquid 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim]BF_4), 1-ethyl-3-methylimidazolium hexafluorophosphate ([emim]PF_6), 1-n-propyl-3-methyl imidazolium tetrafluoroborate ([pmim]BF_4), 1-n-propyl-3-methyl imidazolium hexafluorophosphate ([pmim]PF_6), 1-n-butyl-3-methyl imidazolium tetrafluoroborate ([bmim]BF_4), 1-n-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), 1-n-amyl-3-methylimidazolium tetrafluoroborate ([amim]BF_4), 1-n-amyl-3-methyl imidazolium hexafluorophosphate ([amim]PF_6),1-n-hexyl-3-methylimidazolium tetrafluoroborate ([hmim]BF_4), 1-n-hexyl-3-methylimidazolium hexafluorophosphate ([hmim]PF_6), 1-n-octyl-3-methylimidazolium tetrafluoroborate ([omim]BF_4) and 1-n- octyl -3-methylimidazolium hexafluorophosphate([omim]PF_6) were prepared by the procedures given in the literature[24]. All other chemicals and reagents were of analytical grade and used as obtained.

2.2 Instrumental Analysis and Measurements

Melting points were determined on digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded on a BRUKER-500MHz spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. GC-MS spectra were recorded on HP6890 Gas Chromatograph with a HP5973 Mass Spectrometric Detector. HPLC experiments were performed on a liquid chromatograph (Dionex Softron GmbH, America), consisting of a pump (P680), ultraviolet-visible light detector (UVD) system (170U). The experiments were performed on Zirchrom ODS-1 column, φ 4.6×250 mm.

2.3 General Experimental Procedure for the chloromethylation of aromatic hydrocarbons

All the three-necked flasks were loaded with aromatic hydrocarbon (16.4 mmol), paraformaldehyde (36.3 mmol), 16 mL of concentrated hydrochloric acid and IL (4.92 mmol). The reaction mixture was stirred at 70 ºC for an appropriate time. After the reaction, the mixture was filtered and extracted with methylene chloride (3 × 20 mL). The organic phase were combined and rinsed with saturated $NaHCO_3$ solution (2 × 20 mL) and water (2 × 20 mL). The organic phase was dried with sodium sulfate, filtered and evaporated to dryness *in vacuo*, and the organic residue was resolved in mehtylene chloride again, and analyzed by HPLC. Each product was separated by silica gel column chromatography, and identified by ^{1}H NMR. Residual aqueous catalytic solution was evaporated *in vacuo* to a colorless liquid in 95% yield. The next run was performed under identical reaction conditions.

Representative Data:

1,5-bis(chloromethyl)-2,4-dimethylbenzene: Mp 101 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, H, ArH), 7.05 (s, H, ArH), 4.58 (s, 4H, 2CH_2Cl), 2.39 (s, 6H, 2CH_3); GC-MS: 202, 167, 131, 115, 91, 77.

1-chloromethyl-2,4-dimethylbenzene: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (s, 1H, ArH), 7.00 (s, 2H, ArH), 4.56 (s, 2H, CH_2Cl), 2.37 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); GC-MS: m/z = 154 (M⁺), 119, 115, 103, 91, 77.

1,4-bis(chloromethyl)-2,5-dimethylbenzene: Mp 130 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 2H, ArH), 4.55 (s, 4H, CH_2Cl), 2.37 (s, 6H, 2CH_3);

GC-MS: 202, 167, 131, 115, 91, 77.

1-methoxyl-2,4-bis(chloromethyl)benzene: Mp 53-54 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39-7.40 (d, J = 5 Hz, 1H, ArH), 7.32-7.34 (q, 1H, ArH), 6.86-6.88 (d, J = 10 Hz, 1H, ArH), 4.64 (s, 2H, CH$_2$Cl), 4.59 (s, 2H, CH$_2$Cl), 3.88 (s, 3H, OCH$_3$); GC-MS: 204, 169, 139, 103, 91, 77.

1-chloromethyl-2,5-dimethylbenzene: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.21 (s, 1H, ArH), 7.17 (s, 1H, ArH), 4.65 (s, 2H, CH$_2$Cl), 2.47 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$); GC-MS: m/z = 154 (M$^+$), 119, 115, 103, 91, 77.

1,2-bis(chloromethyl)-4,5-dimethylbenzene: Mp 106 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.17 (s, 2H, ArH), 4.73 (s, 4H, 2CH$_2$Cl), 2.28 (s, 6H, 2CH$_3$); GC-MS: 202, 167, 132, 115, 91, 77.

2.4 General experimental procedure for the recycling ionic liquid and L-proline

The IL was thoroughly extracted with ether to move all organic impurities. Successive reuse of the recovered IL system in the same reaction yielded amounts of product as high as the last cycle. As shown in **Table 1**, no considerable decrease in reactivity and yield was observed after three cycles when the same reaction time was strictly maintained (**entries 3, 14, 15**).

2.5 Calculations

The theoretical study on the experimental results of the aromatic hydrocarbons' chloromethylation by the Gaussian 98 suite of program was developed in this paper for the first time. All calculations were performed with the GAUSSIAN 98 program package[18]. The geometries of all the stationary points were fully optimized at the B3LYP/6-31G* [19] level of theory. The B3LYP functional is composed of Becke's three-parameter hybrid exchange functional (B3), [20-21] as implemented in GAUSSIAN 98[22], and the correlation functional of Lee, Yang, and Parr (LYP).[23] The solvation energies for products and intermediates were computed using solvation model PCM with the permittivities of 78.39, 36.64, 24.55, 10,36 and 2.02, for H$_2$O, CH$_3$CN, CH$_3$CH$_2$OH, CH$_2$ClCH$_2$Cl, and C$_6$H$_{12}$, respectively.

3. RESULTS AND DISCUSSION

The chloromethylation of m-xylene was initially tested at 70 ºC in 5h using 0.3 equiv of [emim]BF$_4$, [emim]PF$_6$, [pmim]BF$_4$, [pmim]PF$_6$, [bmim]BF$_4$, [bmim]PF$_6$, [amim]BF$_4$, [amim]PF$_6$, [hmim]BF$_4$, [hmim]PF$_6$, [omim]BF$_4$ and [omim]PF$_6$. The conversion of m-xylene was 95% using [emim]PF$_6$ (**Table 1, Entry 3**) as catalyst. The conversion is small higher than the conversion(93%) of m-xylene using [emim]BF$_4$ (**Table 1, Entry 2**) as catalyst. When the reaction was performed without ionic liquids, the conversion only reached 63% after 2 days(**Table 1, Entry 1**). As can be seen from **Table 1**, the catalytic activity of these imidazolium-based ILs are reducing when alkyl chain at C-1 of N-methylimidazole ring is increasing. The subsequent experiments revealed that the catalytic activity of hexafluorophosphate is mf mezzo-forte than that of homologous tetrafluoroborate in this reaction.

Having these results in hand, we subjected other aromatic hydrocarbons to these optimized conditions, and the results are listed in **Table 2**. Various aromatic hydrocarbons such as benzene, o-xylene, p-xylene and methylphenate were efficiently converted to the corresponding chloromethyl substituted aromatic hydrocarbons using a catalytic amount of [emim]PF$_6$ at 70 ºC. Yields of these reactions are all higher than yield of reactions using [emim]BF$_4$ as catalyst[17]. Disappointedly, we also did not obtain satisfactory result when the same methods were applied to chlorobenzene, brombenzene and nitrobenzene. The results are same to that of reactions using [emim]BF$_4$ as catalyst[17].

The mechanism of the chloromethylation of aromatic hydrocarbons, as depicted in **Figure 1** is widely accepted. It has six steps and the formation of the intermediate (Carbonium Ion) is the key step [25]. According the reaction mechanism, aromatic ring with higher cloud density attacks the protonated formaldehyde easily. So when aromatic hydrocarbons with electron-donating group are reactants, the yield of product is higher than that with electron-withdrawing group. This point is in good accordance with the experimental outcomes. The aromatic hydrocarbons with electron-withdrawing group don't react in the same reaction conditions such as chlorobenzene, brombenzene and nitrobenzene. The total energies and solvation energies of reactants, intermediates and products in five distinct solvents are collected respectively in **Table 3** and **Table 4**. Because ILs are formed from cations and anions, it is difficult to conduct calculation with the Gaussian 98 suite of program on the interaction of ILs with chemical compounds. Therefore, the theoretical explains for ILs' effect on the reactions can be only done basing on the tendency obtained from the calculation for some selected solvents other than shown directly with calculations.

Table 1. 0.3 equiv of ILs as catalyst for the chloromethylation of m-xylene at 70 ºC.

Entry	ILs	Time (h)	Conv. (%)	A: B(yield %)^{a,b}
1	0	48	63	59: 4
2	[emim]BF$_4$	5	93	85: 8
3	[emim]PF$_6$	5	95	88: 7
4	[pmim]BF$_4$	5	90	84: 6
5	[pmim]PF$_6$	5	92	85: 7
6	[bmim]BF$_4$	5	80	76: 4
7	[bmim]PF$_6$	5	84	77: 7
8	[amim]BF$_4$	5	76	72: 4
9	[amim]PF$_6$	5	80	75: 5
10	[hmim]BF$_4$	5	70	63: 7
11	[hmim]PF$_6$	5	72	65: 7
12	[omim]BF$_4$	5	63	58: 5
13	[omim]PF$_6$	5	66	60: 6
14^c	[emim]PF$_6$	5	95	88: 7
15^d	[emim]PF$_6$	5	94	87: 7

^{a} A is 1,5-bis(chloromethyl)-2,4-dimethylbenzene, B is 1-chloromethyl-2,4-dimethylbenzene.
^{b} A: B for each sample was determined by HPLC.
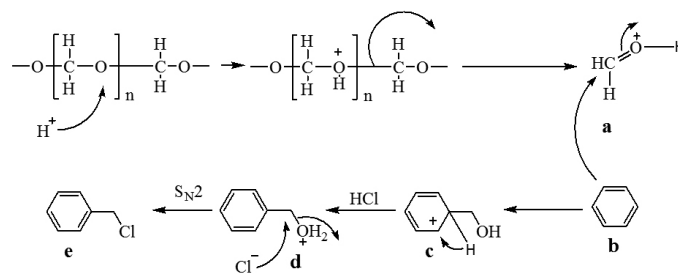^{c} The second run.^{d} the third run.

Figure 1. The mechanism of the chloromethylation of aromatic hydrocarbons.

As shown in **Table 4**, the solvation energy (negative value) decreases with the increasing polarity of the solvent. This clearly indicates that reactants, intermediates and products become more stable when polarity of solvent increases. Because the polarity of the water is highest among conventional solvents, the water is suitable for the reaction. But concentration of concentrated hydrochloric acid will be reduced using water as solvent, it make against reaction. So we chose IL as reaction solvent. This can be rationalized that the polarity of IL is the highest among all solvents considered and ILs are formed from large organic cations and inorganic anions, which can promote the stability of intermediates possessing partial charges. Furthermore, concentration of concentrated hydrochloric acid will be not reduced using IL as solvent. Thus, the reactants, intermediates and products in IL are more stable compared with those in other organic solvents. Solvents play a crucial role in the reaction by stabilizing ionic charges and providing an alternative lower energy pathway by which the reaction may proceed. Hence, the chloromethylation of aromatic hydrocarbons in ILs can be definitely promoted.

Table 2. [emim]PF$_6$ as catalyst for the chloromethylation of aromatic hydrocarbons at 70 ºC.
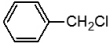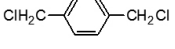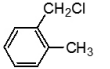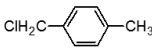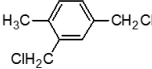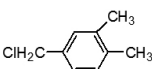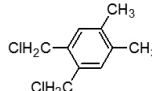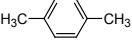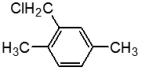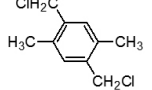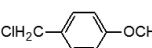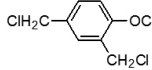
Entry	aromatic hydrocarbon	[emim] PF$_6$(equiv.)	Time (h)	Yield (%)	Products and yields (%)
1		0.3	5	78	16 62
2		0.3	5	98	7 28 63
3		0.3	5	92	20 72
4		0.3	5	92	41 51
5		0.3	5	95	16 79
6		1.0	48	0	-----
7		1.0	48	0	-----

Table 3. The calculated energies (Hartree) of the reactants, intermediates and products in five distinct solvents.

	H$_2$O	CH$_3$CN	CH$_3$CH$_2$OH	ClCH$_2$CH$_2$Cl	C$_6$H$_{12}$
a	-114.9066935	-114.9045998	-114.9026953	-114.8949163	-114.8433846
b	-232.2539379	-232.2537674	-232.2536293	-232.2530922	-232.2504721
c	-347.1720992	-347.1703598	-347.1688765	-347.1627849	-347.1233882
d	-347.2008509	-347.1985801	-347.1959950	-347.1891559	-347.1426865
e	-731.1689354	-731.1686444	-731.1684247	-731.1675625	-731.1633150

Table 4. The solvation energies of the reactants, intermediates and their products in five distinct solvents (kcal mol^{-1}).

	H$_2$O	CH$_3$CN	CH$_3$CH$_2$OH	CH$_2$CH$_2$Cl$_2$	C$_6$H$_{12}$
a	-80.37	-78.90	-77.54	-72.11	-38.42
b	-3.69	-3.56	-3.45	-3.04	-1.18
c	-60.86	-59.64	-58.62	-54.47	-28.80
d	-74.85	-73.10	-70.96	-65.81	-32.27
e	-6.30	-6.05	-5.88	-5.19	-2.04

5. CONCLUSION

In summary, imidazolium-based ILs have been proved to be an effective promoter for the chloromethylation of aromatic hydrocarbons. Further study has revealed that ionic liquids can be reused at least three times with comparable yields. The present method has many obvious advantages compared to previous methods, such as environmentally more benign, the ease of product isolation, the simplicity of methodology, the high yield, the generality, the convenience of preparing the ILs using much cheaper starting material, and the potential for recycling of ionic liquid. Moreover, enhanced rate resulting from IL-based activation was speculated and proved by calculations with the Gaussian 98 suite of program, as well as reagents' reactivity which is different from that in traditional organic solvents. Further studies aimed at exploring the scope of organocatalytic reactions in ILs are in progress.

REFERENCE

1   R.C.Fuson, C.H. McKeever, in Organic Reactions, John Wiley, New York.1.1943, pp.63-90.
2   G.A.Olah, in Friedel Crafts and Related Reactions, John Wiley, New

York, 1964, Vol. 2, part 2, pp.659-784.

3   J.H.Wood, M.A.Perry, C.C.Tung, J. Am. Chem. Soc., 72, 2989-2991,(1950)

4   J.H.Wood, M.A.Perry, C.C.Tung, J. Am. Chem. Soc. 72, 2992-2995, (1950)

5   C.D.Shacklett, H.A. Smith, J. Am. Chem. Soc. 73, 766-770, (1951)

6   T. Sasaki, Y. Hasebe, S.Okada, T. Arai, Jpn. Kokai Tokkyo Koho JP63-048234, 1988.

7   M.Gerisch, J.R.Krumper, R.G.Bergman, T. Don Tilley, Organometallics. 22, 47-50, (2003)

8   Green Chemistry. Frontiers in Benign Chemical Synthesis and Processes, ed. P. T. Anastas and T. C. Williamson, Oxford University Press, Oxford, 1998.

9   T. Kishida, T.Yamauchi, Y. Kubota, Y. Sug, Green Chem. 6, 57-60, (2004)

10 T. Nishida, Y. Tashiro, M.Yamamoto, J. Fluorine Chem. 120, 135-138, (2003)

11 J.S.Wilkes, J.A.Levisky, R.A.Wilson, C.L.Hussey, Inorg. Chem. 21, 1263-1265, (1982)

12 (a) R. Sheldon, Chem. Commun. 2399-2402, (2001); (b) C.J. Admas, M.J. Earle, G. Roberts, K.R.Seddon, Chem. Commun. 2097-2100, (1998); (c) C. M. Gordon, A. McCluskey, Chem. Commun. 1431-1433, (1999); (d) Ch.Admas, M.J.Earle, K.R.Seddon, Green Chem. 2, 21-24, (2000)

13 J.G. Huddleston, H.D.Williams, R.P. Swatloski, A.E. Visser, R.D.Rogers, Chem. Commun., 1765, (1998)

14 a) V. I. Paˆrvulescu, Ch. Hardacre, Chem. Rev. 107, 2615-2665, (2007); b) J. P. Hallett , T. Welton, Chem. Rev. 111, 3508-3576, (2011); c) N.V. Plechkovaa, K.R. Seddon, Chem. Soc. Rev. 37, 123-150, (2008); d) B. Wu, W. W. Liu, Y.M. Zhang, H. P. Wang, Chem. Eur. J. 15, 1804 – 1810, (2009); e) S.K.Tang, G. A. Bakerb, H. Zhao, Chem. Soc. Rev. 41, 4030–4066, (2012)

15 (a) K.S.Yeung, M.E.Farkas, Z.L. Qiu, Z.Yang, Tetrahedron Lett. 43, 5793-5800, (2002); (b) S.J. Nara, J.R. Harjani, M.M.Salunkhe, J. Org. Chem. 66, 8616-8620, (2001)

16 (a) Y.R. Jorapur, C.H. Lee, D.Y. Chi, Org. Lett. 7, 1231-1236, (2005); (b) H.Y. Shen, Z.M.A. Judeh, C.B.Ching, Tetrahedron Lett. 44, 981-988, (2003); (c) E.J.Corey, Y.Bo, J. Busch-Peterson, J. Am. Chem. Soc. 120, 13000-13006, (1998)

17 Y. Wang, Zh.-C.Shang, T.-X. Wu, Synthetic Communications. 36, 3053-3059, (2006)

18 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Jr. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M.W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian 98, Gaussian, Inc.: Pittsburgh, PA, 1998.

19 (a) R. Ditchfield, W. J. Hehre, J. A. Pople, J. Phys. Chem. 54, 724-728, (1971); (b) W. J. Hehre, R. Ditchfield, J. A. Pople, J. Phys. Chem. 56, 2257-2260, (1972); (c) P. C. Hariharan, J. A. Pople, Theor. Chim. Acta. 28, 213, (1973)

20 A. D.Becke, J. Chem. Phys. 98, 1372-1376, (1993)

21 A. D.Becke, J.Chem. Phys. 98, 5648-5651, (1993)

22 P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, J. Phys. Chem. 98, 11623-11627, (1994)

23 C. Lee, W. Yang, R. G. Parr, Phys. Rev. B. 37, 785, (1987)

24 (a) P.A.Z.Suarez, J.E.L.Dullius, S.Einloft, R.F.de Souza, J.Dupont, Polyhedron. 15, 1217, (1996); (b) P.Bonhote, A.-P. Dias, N. Papageorigu, K. Kalyanasundaram, M.Gratzel, Inorg. Chem. 35, 1168, (1996); (c) K. R. Seddon, A. Stark, M.-J. Torres, Pure. Appl. Chem. 72, 2275, (2000); (d) G.S.Owens, M.M.Abu-Omer, J. Mol. Catal. A: Chem. 187, 2-6, (2002)

25 (a) Y. Sekine, V. J. Boekelheide, J. Am. Chem. Soc. 103,1777-1780, (1981); (b) K. Ito, Y. Ohba, E. Shinagawa, S. Nakayama, S. Takahashi, K. Honda, H. Nagafuji, A. Suzuki, T. Sone, J. Heterocycl. Chem. 37, 1479-1482, (2000)