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A Base Promoted Synthesis of *N*,*N*-dimethylformamidines

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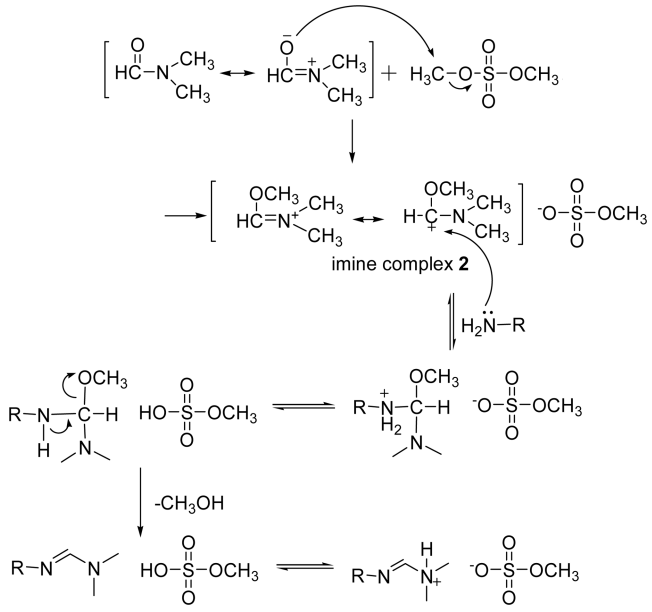
As a kind of important intermediates, *N*,*N*-dimethylformamidines (**1**) has been widely used to synthesize nitrogen-containing heterocyclic compounds such as benzoimidazole,[1] quinoline,[2,3] indole[4] and quinazolines.[5] In recent years, the synthesis of various quinazolines,[6] as inhibitors of tyrosine kinase,[7] has been a focus for medicinal chemists. Meanwhile Stephan Enthaler's group reported that **1** as versatile ligands exhibited potential in the zinc-catalyzed hydrosilylation of carbonyl compounds and the iron-catalyzed epoxidation of olefins.[8] Although **1** has presented various important uses, only three reported synthesis methods were mainly used. Using *N*,*N*-dimethylformamide (DMF) and different arylamines as starting materials in the presence of Vilsmeier–Haack reagent ($POCl_3$) can give **1** in moderate yields.[8-10] This method requires anhydrous and inert atmosphere conditions, and longer reaction time, also the pollutant is produced from $POCl_3$. **1** could be also prepared in shorter reaction time from primary amines, DMF and sulfonyl chlorides.[11] However, good selectivity of formamidine could be obtained only in the presence of 2-pyridinesulfonyl chloride. And by-products, sulfonamides, are formed from amines and other sulfonyl chlorides in this route. The synthesis strategy of **1** through the condensation of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) and arylamines is used in the highest frequency,[12-14] because of higher yield of **1** and convenience work-up. However this method in most cases still demands longer reaction time and relative high reaction temperature.[15] Therefore, development of a mild, efficient and low environmental impact synthetic strategy is still in strong demand. We herein report a base promoted synthesis for **1** through the nucleophilic reaction of arylamines bearing strong electron withdrawing group at *o*-position and imine complex produced from DMF and dimethyl sulfate.

Considering DMF can react with dimethyl sulfate to yield imine complex $HCONMe_2Me_2SO_4$ (**2**) under free-solvent condition.[16] We supposed that the nucleophilic reaction of arylamines with **2** should straight supply the salts of **1** (see Scheme 1). Subsequently, simple neutralization of the salts will give **1**. To the best of our knowledge, only four primary amines such as CH_3NH_2,[17] $PhNH_2$,[18] cyclohexylamine and *t*-Bu-NH_2,[19] were used to react with the imine complex, and to yield corresponding *N'*-alkyl-*N*,*N*-dimethylformamidines, respectively. To investigate the suitability of the reaction, we used various primary amines as nucleophilic reagents to react with **2**. The generated salts were alkalized with sodium carbonate solution, and gave free *N'*-alkyl-*N*,*N*-dimethylformamidines. The results listed in Table 1 reveal that most primary amines could give target compounds. Especially, the reactions of fatty amines such as benzylamine and *n*-butylamine with imine complex **2** were very fast with heat release to lead complex products. When the reaction mixture was cooled to −10 °C, these fatty amines still gave products **1** in 89.2% and 82.2% (see entry 12 and 13 in Table 1). Aniline also showed very high reactivity and gave quantitative reaction at room temperature (entry 1 in Table 1). Some substituted arylamines, especially which bearing strong electron withdrawing groups such as nitro group, exhibited lower reactivity (entry 5, 14 and 15 in Table 1). Unfortunately, arylamines with strong electron withdrawing group such as nitro, cyano-group at *o*-position did not give target compounds (entry 16-19 in Table 1), even with prolonging reaction time to 12 h and increasing reaction temperature to 50 °C. The

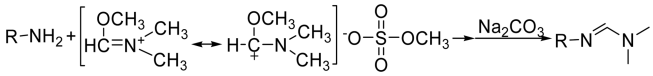


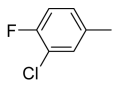
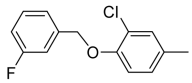
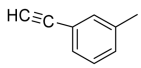
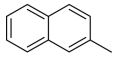
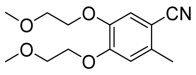
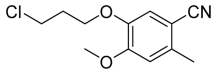
Scheme 1. The synthetic reaction for the salts of **1**.

failure of the reaction should impute on the decreased nucleophilic capability of amino group from strong electron withdrawing effect of substituent, the formation of hydrogen bond between H of amine and nitro or cyano-group at *o*-position, and the steric hindrance.

On basis of above results and cognition, we tried to find a method for preparation of **1** from arylamines bearing strong electron withdrawing group at *o*-position through the route as shown in Scheme 1. If the base was added to the mixture of arylamines and **2**, the elimination process of proton might be promoted in the step of generating methanol. In order to prepare *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine, an important intermediate for synthesis of antitumor drug erlotinib, we explored the nucleophilic reaction of 2-cyano-4,5-dimethoxyethoxylaniline with **2** as a model reaction in the presence of base. Initial, sodium hydroxide was added to the solution of 2-cyano-4,5-dimethoxyethoxylaniline and **2** in toluene. The mixture was stirred and tracked by TLC for 9 h at room temperature to arylamine exhaustion, *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine was found in the mixture from GC-MS analysis. The result approved our hypothesis and encouraged us to further optimize the reaction. Thus various bases as promote agents and other factors, such as solvent, temperature, reaction time and molar ratio of imine complex to arylamine *etc*., were investigated in the reaction. The results shown in Table 2 indicate that the basicity of added bases affect obviously on the reaction (entry 1-5 in Table 2). With increasing basicity, the yields presented increasing tend besides shortening reaction time. The best yield was obtained in the presence of sodium methoxide. Thus sodium methoxide was used as the best promote reagent to optimize other reaction condition. When toluene, ethyl acetate, methylene chloride and chloroform were used as reaction medium (entry 5-8 in Table 2) respectively, the reaction in toluene gave the highest yield in 90.4%. Then, the reaction temperature was investigated at 20, 40 and 60 °C. The results suggested that increasing temperature led to shorter reaction time from 3 h to 2 h, deduce from TLC tracking, meanwhile the complex components were found in the result mixture, and the yield of target product decreased from 90.4 to 66.1 and 73.2% (entry 5, 9 and 10 in Table 2). Decreasing molar ratio of imine complex **2** to 2-cyano-4,5-dimethoxyethoxylaniline resulted in longer reaction time and lower yields (entry 5 and 11-13 in Table 2). Thus a optimized condition was obtained as follows: the mixture of 2-cyano-4,5-dimethoxyethoxylaniline (1.52 g, 5.7 mmol), imine complex (4.49 g, 22.6 mmol) and sodium methoxide (0.23 g, 4.3 mmol) in toluene (20 mL) was stirred for 3 h at room temperature (20 °C).

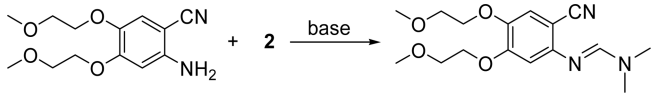
Table 1. Synthesis of *N*′-alkyl-*N*,*N*-dimethylformamidines[a]



Entry	R	Yield[a] (%)
1	C_6H_5-	~100
2	*p*-MeC_6H_4-	78.8
3	*p*-$MeOC_6H_4$-	61.2
4	*m*-$MeOC_6H_4$-	65.7
5	*o*-$MeOC_6H_4$-	56.2
6	*p*-BrC_6H_4-	68.3
7		78.0
8		54.8
9		46.0
10		72.4
11		64.6
12	$PhCH_2$-	89.2[b]
13	*n*-Bu-	82.2[b]
14	*m*-$O_2NC_6H_4$-	53.9
15	*p*-$O_2NC_6H_4$-	10.1
16	*o*-$O_2NC_6H_4$-	None
17	2,4-$(O_2N)_2C_6H_3$-	None
18		None
19		None

[a]Isolated yield. [b]The reaction was carried out at −10 °C.

Table 2. Optimization of the reaction conditions for the preparation of *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine[a]



Entry	Base	Solvent	Reaction time (h)	Temperature (°C)	Molar ratio[b]	Yield[c] (%)
1	NaOH	toluene	9	20	4	31.2
2	Na_2CO_3	toluene	9	20	4	26.8
3	K_2CO_3	toluene	9	20	4	14.8
4	$KOCH_3$	toluene	3	20	4	89.1
5	$NaOCH_3$	toluene	3	20	4	90.4
6	$NaOCH_3$	AcOEt	3	20	4	67.2
7	$NaOCH_3$	CH_2Cl_2	3	20	4	28.4
8	$NaOCH_3$	$CHCl_3$	3	20	4	31.7
9	$NaOCH_3$	toluene	2	40	4	66.1
10	$NaOCH_3$	toluene	2	60	4	73.2
11	$NaOCH_3$	toluene	4	20	3	76.2
12	$NaOCH_3$	toluene	4	20	2	61.2
13	$NaOCH_3$	toluene	4	20	1	17.9

[a]The reaction condition: the mixture of 2-cyano-4,5-dimethoxyethoxylaniline (1.52 g, 5.7 mmol), imine complex **2** and base (4.3 mmol) in indicated solvent (20 mL) was stirred with TLC tracking to the exhaust of 2-cyano-4,5-dimethoxyethoxylaniline. [b]Molar ratio of imine complex **2** to 2-cyano-4,5-dimethoxyethoxylaniline. [c]Isolated yield.

Herein DMF and Me_2SO_4 were used as raw materials to generate imine complex **2** (see Scheme 1). It is well known that the reaction of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) with arylamines such as 2-cyano-4,5-dimethoxyethoxylaniline *etc*. can also yield *N*′-aryl-*N*,*N*-dimethylformamidines,[12] meanwhile the commercial available DMF-DMA is just prepared through the reaction of sodium methoxide with imine complex **2** generated from DMF and Me_2SO_4.[20,21] Thus we doubted that DMF-DMA might be generated in situ from imine complex **2** and added sodium methoxide in our process. In order to get an answer, the reaction was tracked by taking sample at regular intervals from the reaction mixture to analyze by GC-MS. The results are shown in Figure 1. The peaks of net DMF-DMA, 2-cyano-4,5-dimethoxyethoxylaniline and *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine showed at 4.4, 11.3 and 12.9 min. in chromatogram (see Figure 1(a) and 1(d)), respectively. No DMF-DMA was found in the reaction mixture from beginning to end. This indicated obviously that the formation of *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine in our process was not through DMF-DMA way. On the other hand, although many *N*′-aryl-*N*,*N*-dimethylformamidines can be prepared with DMF-DMA, in fact, the synthesis of DMF-DMA still needs DMF, Me_2SO_4 and sodium methoxide as raw materials. Therefore our straight protocol promoted by base exhibits obvious advantages such as low cost, high efficiency and low environmental impact. As shown in Figure 1, to arylamines bearing strong electron withdrawing group at *o*-position, the base plays an important role for the formation of target product. No *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine was found in the mixture of 2-cyano-4,5-dimethoxyethoxylaniline and **2** in absent of $NaOCH_3$, even after the mixture was stirred for 0.5 h (Figure 1(b)). This is consistent with the result from entry 16-19 in Table 1. After adding $NaOCH_3$, target product was starting to form, and with prolonging reaction time, the increasing of target product was found in the reaction mixture (see Figure 1(c) and 1(d)). After 3 h, by-product (peak at 11.6 min.) was also obviously formed (see Figure 1(f)).

The reported method herein should also be suitable to the preparation of other *N*′-aryl-*N*,*N*-dimethylformamidines from arylamines bearing strong electron withdrawing group at *o*-position. We expanded the reaction to other arylamines in the same condition except little modifying molar ratio. The results shown in Table 3 indicate that all tested arylamines can give *N*′-aryl-*N*,*N*-dimethylformamidines in good to excellent yields even with substrates bearing strong electron withdrawing group such as cyano-group at *o*-position. However *o*-nitroaniline and 2,4-dinitroaniline still gave lower yields, the further improvement is underway.

In conclusion, this report supplies a base promoted synthesis of *N*′-aryl-*N*,*N*-dimethylformamidines straight from arylamines bearing strong electron withdrawing group at *o*-position and imine complex from DMF and Me_2SO_4. The key advantage of the procedure is to avoid the preparation of *N*,*N*-dimethylformamide dimethyl acetal from DMF and Me_2SO_4. Using this method, some important intermediates shown as entry 1-4, 9-11 in Table 3 were efficiently prepared. With these intermediates in hand, various antitumor drugs containing quinazoline moiety such as gefitinib, erlotinib and lapatinib *etc*. can be synthesized conveniently.

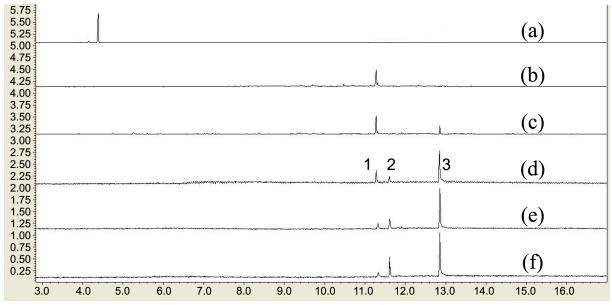


Figure 1. The chromatogram of GC-MS analysis. a. net DMF-DMA; b. the mixture of 2-cyano-4,5-dimethoxyethoxylaniline and **2** was stirred for 0.5 h; c-f. the reaction mixture after adding $NaOCH_3$ for 0.5 h, 1 h, 2 h and 3 h, respectively. Peak 1. 2-cyano-4,5-dimethoxyethoxylaniline; peak 2. by-product; peak 3. *N*′-(2-cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine.

Experimental Section

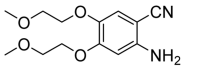
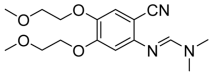
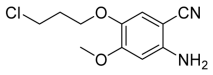
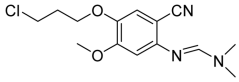
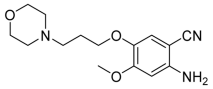
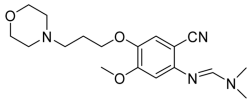
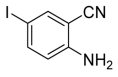
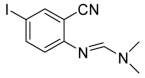
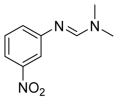
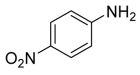
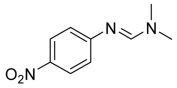
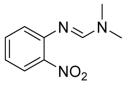
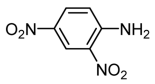
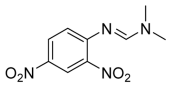
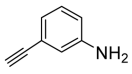
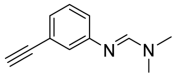
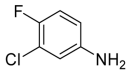
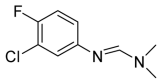
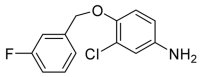
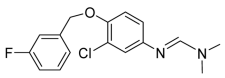
General Methods. ^1H NMR spectra were recorded on 300 MHz spectrometer. ^{13}C NMR spectra were recorded on 75 MHz spectrometer. GC-MS analysis was performed using EI-quadrupole mass analyzer on Shimadz GCMS-QP2010 with RTX-1MS capillary column (30 m × 0.25 mm × 0.25 μm). High resolution mass spectra (HRMS) were performed on a MaXis UHR-TOF with direct injection of the sample.

Synthesis of Imine Complex (2). The mixture of Me_2SO_4 (2.53 g, 20.0 mmol) and DMF (1.47 g, 20.0 mmol) was refluxed with stirring at 70 °C for 3 h. The result mixture was not further purified and straight used as imine complex in next step.

Synthesis of *N*′-Alkyl-*N*,*N*-dimethylformamidine. The mixture of 4.00 g (20 mmol) imine complex **2**, 20 mmol primary amine and 20 mL toluene was stirred at room temperature for 40 min. After filtration, the filter cake was dissolved in water and alkalized with sodium carbonate solution to pH 10-11. The mixture was extracted with CH_2Cl_2 (10 mL × 3), the organic phase was dried with anhydrous sodium sulfate. After removing solvent, free *N*′-alkyl-*N*,*N*-dimethylformamidine were obtained.

Base Promoted Synthesis of *N*′-Aryl-*N*,*N*-dimethylformamidine. The mixture of 4.00 g (20 mmol) imine complex **2**, 5 mmol arylamine, 0.22 g (4 mmol) sodium methoxide and 20 mL toluene was stirred at room temperature for 3 h. Volatile substances were removed in vacuum with rotary evaporator. 20 mL of H_2O was added to the residue and adjusted pH to 3 with 2 M H_2SO_4. The result mixture was extracted with 10 mL CH_2Cl_2 to remove insolubility organic compounds. To aqueous phase was added 20% NaOH to pH 10, and extracted with CH_2Cl_2 (10 mL × 2). The organic phase was dried with anhydrous sodium sulfate. After removing

Table 3. Synthesis of *N′*-aryl-*N*,*N*-dimethylformamidines in the presence of MeONa

Entry	Substrate	Product	Yield[a] (%)
1			90.5
2			78.3
3			81.9
4			89.1
5			96.3
6			97.3
7			23.8
8			6.4
9			86.6
10			100.0
11			97.1

[a]Isolated yield.

solvent, free *N′*-aryl-*N*,*N*-dimethylformamidine was obtained.

All obtained products were identified by MS, ^{1}H NMR and ^{13}C NMR spectra. Selected spectral data for synthesized compounds from 2-cyano arylamines are given as follows.

***N′*-(2-Cyano-4,5-dimethoxyethoxylphenyl)-*N*,*N*-dimethylformamidine (entry 1 in Table 3):** Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 6H), 3.43 (s, 6H), 3.75 (d, 4H, J = 8.3 Hz), 4.15 (d, 4H, J = 8.3 Hz), 6.49 (s, 1H), 7.00 (s, 1H), 7.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 153.6, 151.5, 143.9, 118.9, 118.2, 105.5, 96.9, 70.9, 70.6, 69.5, 68.3, 59.1, 59.0, 40.2, 34.3.

***N′*-[4-(3-Chloropropoxy)-2-cyano-5-methoxyphenyl]-*N*,*N*-dimethylformamidine (entry 2 in Table 3):** White solid, mp 105.4-106.7 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.24-2.29 (m, 2H), 3.06 (s, 6H), 3.76 (t, 2H, J = 6.1 Hz), 3.87 (s, 3H), 4.10 (t, 2H, J = 5.7 Hz), 6.46 (s, 1H), 6.98 (s, 1H), 7.58 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 32.2, 34.5, 40.3, 41.4, 55.9, 66.4, 96.2, 104.4, 116.9, 119.1, 143.6, 151.6 153.8, 154.2; HRMS *m*/*z*: $[M+H]^+$: 296.1160 (calcd. 296.1162).

***N′*-[2-Cyano-5-methoxy-4-(3-morpholinopropoxy)phenyl]-*N*,*N*-dimethylformamidine (entry 3 in Table 3):** White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (m, 2H), 2.33 (m, 6H), 2.93 (s, 6H), 3.58 (bs, 4H), 3.74 (s, 3H), 3.90 (t, 2H, J = 5.9 Hz), 6.35 (s, 1H), 6.85 (s, 1H), 7.48 (s, 1H).

***N′*-(2-Cyano-4-iodophenyl)-*N*,*N*-dimethylformamidine (entry 4 in Table 3):** Yellow solid, mp 54.0-55.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.65 (d, 1H, J = 8.5 Hz), 7.59 (s, 1H), 6.70 (d, 1H, J = 8.5 Hz), 3.08 (s, 6H); MS (*m*/*z*): 299 $[M]^+$.

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References

1. Dohle, W.; Staubitz, A.; Knochel, P. *Chem. Eur. J*. **2003**, *9*, 5323.
2. Yoon, D. S.; Han, Y.; Stark, T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775.
3. Heath, J. A.; Mehrotra, M. M.; Chi, S.; Yu, J. C.; Hutchaleelaha, A.; Hollenbach, S. J.; Giese, N. A.; Scarborough, R. M.; Pandey, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4867.
4. Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819.
5. Domarkas, J.; Dudouit, F.; Williams, C.; Qiu, Q.; Banerjee, R.; Brahimi, F.; Bertrand, J. J. *J. Med. Chem*. **2006**, *49*, 3544.
6. Wissner, A.; Floyd, M. B.; Johnson, B. D.; Fraser, H.; Ingalls, C.; Nittoli, T.; Dushin, R. G.; Discafani, C.; Nilakantan, R.; Marini, J. *J. Med. Chem*. **2000**, *48*, 7560.
7. Morphy, R. *J. Med. Chem.* **2010**, *53*, 1413.
8. Enthaler, S.; Schroeder, K.; Inoue, S.; Eckhardt, B.; Junge, K.; Beller, M.; Driess, M. *Eur. J. Org. Chem.* **2010**, *2010*(25), 4893.
9. Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
10. Meyers, A. L.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E., Jr. *J. Org. Chem.* **1985**, *50*, 1019.
11. Cai, L.; Han, Y.; Ren, S.; Huang, L. *Tetrahedron* **2000**, *56*, 8253.
12. Chandregowda, V.; Rao, G. V.; Reddy, G. C. *Organic Process Research & Development* **2007**, *11*, 813.
13. Chandregowda, V.; Rao, G. V.; Kush, A. K.; Reddy, G. C. *WO 2007138612*, 2007-12-06.
14. Tang, B.; Zhu, G. R.; Zhang, L.; Bai, X. F. *CN 201110073343*, 2011-03-26.
15. Meng, G.; Sha, Y. W.; Zhang, R.; Bai, N. *Chinese Chemical Letters* **2011**, *22*, 1043.
16. Bredereck, H.; Effenberger, F.; Simchen, G. *Chemische Berichte* **1963**, *96*, 1350.
17. Bredereck, H.; Effenberger, F.; Simchen, G. *Argew. Chem*. **1962**, *74*, 353.
18. Bredereck, H.; Effenberger, F.; Simchen, G. *Angew. Chem*. **1961**, *73*, 493.
19. Meyers, A. I.; Ten Hoeve, W. *J. Am. Chem. Soc*. **1980**, *102*, 7125.
20. Feng, R. L; Gong, P.; Fang L.; Hong, W. *Chemical Research in Chinese Universities* **2005**, *20*(2), 177.
21. Salomon, R. G.; Raychaudhuri, S. R. *J. Org. Chem.* **1984**, *49*(19), 3659.