Silica-Alumina Catalyst Support, an Efficient Catalyst for Synthesis of Halogen Substituted 2,6-Bis(imino)pyridines

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Abstract: Silica-alumina catalyst support was found to be an efficient catalyst for the condensation reaction of 2,6-, 2,5-, and 2,4-di-fluoroaniline and *ortho*-halogen-aniline with 2,6-diacetylpyridine to afford corresponding 2,6-bis(imino)pyridines in 56–75% isolated yields under extremely mild reaction conditions. The catalyst can be recovered and reused

Key words: silica-alumina catalyst support, halogen substituted 2,6-bis(imino)pyridine, condensation reaction

Recently, a class of iron and cobalt complexes bearing bis(imino)pyridines were reported by Brookhart¹⁻³ and Gibson.^{4,5} These complexes are highly active catalysts for ethylene polymerization and oligomerization in the presence of MAO(methylaluminoxane). All reported bis(imiexclusively no)pyridines alkyl-substituted are compounds. To our knowledge, there is no report about synthesis of halogen substituted bis(imino)pyridines in literature. Due to electronic and steric effects of halogen, it is interesting to study the relationship between catalyst efficiency and halogen substituents. In our previous work, we synthesized a series of di-chloro- and di-bromo-substituted 2,6-bis(imino)pyridines and their iron and cobalt complexes.⁶ The investigation of their catalytic activities in ethylene polymerization has shown that these iron and cobalt complexes are very active.⁷ Also we found the complex bearing 2,6-di-fluoro-substituted iron(II) bis(imino)pyridine(1a) oligometized ethylene to α -olefins with very high activity and selectivity.8 In addition, halogen-substituted ketimines are important intermediates or precursors for preparing pyrimidine with polyhaloalkyl group,9 which are of great interest because of their herbicidal, fungicidal, antibiotic, antiviral or antineoplastic properities,¹⁰ electron transport materials in positive charge electrophtography,^{13c} spiro-heterocycles of indole derivatives.^{13b} Also these ketimines can be used as adhesive, crosslinking agent, and curing agent in resin.¹¹

However, in most case those halogen substituted 2,6bis(imino)pyridines cannot be prepared in the same manner as reported alkyl substituted ones.^{2,3,5} Moreover, in the case of the reaction of halogen-substituted aniline with aromatic ketone, it needs much stronger reaction conditions such as at 210 °C,¹² catalyzed by AlCl₃, ZnCl₂, or *p*-TsOH

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in refluxing chlorobenzene, toluene, xylene, or 1,2,3,4tetrahydronnaphthalene with removal of water,¹³ and promoted by $TiCl_4$ in refluxing solvents,¹⁴ often with low to moderate yield. It promotes us to find a new method to synthesize di-fluoro- and *ortho*-halogen-substituted 2,6bis(imino)pyridines.

The condensation reaction of 2,6-dihalogenaniline with 2,6-diacetylpyridine, catalyzed by *p*-TsOH in fluxing toluene, won't go on without removing water by azeotropic distillation.⁶ Because the halogen substituted 2,6-bis(imino)pyridines at high temperature are not stable in air, the condensation reactions were sensitive to temperature. Synthesis of di-fluoro-substituted 2,6-bis(imino)pyridine shown the same property. At a higher temperature the reaction produced complicated mixture and the yield decreased steeply (entries 1, 2, Table 1). It must be noted that the product should be purified by recrystallization, Attempted separation of the product by flash column led to a sharp decrease of yield.¹⁵

A number of reactions have been found to proceed smoothly by the catalysis of rare earth(III) triflates.¹⁶ Several $Ln(OTf)_3$ (Ln = La, Gd, Yb) were examined to catalyze this condensation reaction. Gd(OTf)₃ provided the best result of 44% yield (entry 7, Table 1). In the case of La(OTf)₃, a sluggish reaction was observed in THF and CH₂Cl₂ (entries 4-6, Table 1). A stronger Lewis acid $Gd(OPf)_3$ (Pf = perfluorooctanesulfonate)¹⁷ was also tested with a dramatic decrease of yield (entry 9, Table 1). Fortunately, we found silica-alumina catalyst support (Grade 135) combination with 4 Å molecular sieves¹⁸ could catalyze this condensation reaction at 30 °C with satisfied 65% yield, after simple filtering and vacuuming.¹⁹ The mixture of Si-Al-135 and 4 Å MS powder recovered could be reactivated by heating at 200 °C in vacuo without reducing its reactivity (entry 10, Table 1). Increasing the calcination temperature from 200 °C to 500 °C, the yield was decreased from 65% to 31%. In solvents other than toluene, it gave much lower yield (entries 10-12, Table 1). Especially, when THF was used, only half condensation product 2 was obtained in 41% yield (Figure 1). Compound 2a may be an excellent ligand, because it was reported the half condensed 2,6-di-i-Praniline analogous exhibited high activity for ethylene polymerization.²⁰

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 Table 1
 The Optimization of the Condensation Reaction Conditions

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	N + F		cat. vent, 24 h				
1 equiv 2.4 equiv							
Entry	Catalyst	Amount	Solvent	T (°C)	Yield (%) ^a		
1	<i>p</i> -TsOH	8 g/mol	Toluene	Reflux	13		
2	<i>p</i> -TsOH	8 g/mol	Benzene	Reflux	24		
3	HOAc	Cat.	Ethanol	Reflux	None		
4	La(OTf) ₃ 4 Å MS	5 mol%	Toluene	30	21		
5	La(OTf) ₃ 4 Å MS	5 mol%	THF	30	4		
6	La(OTf) ₃ 4 Å MS	5 mol%	CH ₂ Cl ₂	30	9		
7	Gd(OTf) ₃ 4 Å MS	5 mol%	Toluene	30	44		
8	Yb(OTf) ₃ 4 Å MS	5 mol%	Toluene	30	40		
9	Gd(OPf) ₃ 4 Å MS	5 mol%	Toluene	30	9		
10	Si-Al-135 4 Å MS	80 g/mol	Toluene	30	65 (64, ^b 59, ^c 57 ^d)		
11	Si-Al-135 4 Å MS	80 g/mol	THF	30	0 (41) ^e		
12	Si-Al-135 4 Å MS	80 g/mol	CH ₂ Cl ₂	30	13		
Inclosed wield							

^a Isolated yield.

^b The second run.

^c The third run.

^d The fourth run.

^e Yield of half condensation product 2a.

We also tested three other acidic aluminosilicates of zeolite H-Beta,^{21a} zeolite H-Y^{21b} and Si-Al(II)^{21c} which has smaller specific surface area than Si-Al-135 (Table 2). For small steric aniline as 2-fluoroaninline and 2,6-difluoroaninline, there is a trend in the aluminosilicates with similar structure, the yields of Si-Al-135 and Si-Al(II) increase with the increase of the specific surface area, so do the yields of zeolite H-Beta and zeolite H-Y. Zeolite H-Y could give comparative results with Si-Al-135. For larger steric aniline as 2-bromoaniline, Si-Al(II), zeolite H-Beta and zeolite H-Y all gave a mixture of mono- and di-condensation products with the ratio of 1.20, 0.65 and 0.76 (mono- to di-). While Si-Al-135 could give 75% yield. These results were directly related to their specific surface area and pore size.^{18,21} It is possible that catalysts with larger speific surface area and pore diameter could give better results.

 Table 2
 Screening of Some Acidic Aluminosilicates

	equiv 2.4 equiv	Cat. (8 g/mol) 4 Å MS Toluene, 24 h 30~40 °C	N II N Ar
Entry	Aniline	Catalyst	Yield (%)
1	2-fluoroaniline	Si-Al-135	56 ^b
2		Si-Al(II)	46
3		Zeolite H-Y	67
4		Zeolite H-Beta	36
5	2,6-difluoroaniline	Si-Al-135	65 ^c
6		Si-Al(II)	39
7		Zeolite H-Y	52
8		Zeolite H-Beta	36
9	2-bromoaniline	Si-Al-135	75
10		Si-Al(II)	24 ^d
11		Zeolite H-Y	29 ^d
12		Zeolite H-Beta	33 ^d
a Isolat	ed vield		

^a Isolated yield.

^b Data taken from Table 3.

^c Data taken from Table 1.

^d Calculated from ¹H NMR.



Figure 1

A series of *ortho*-halogen substituted anilines were screened in the condensation reactions catalyzed by Si-Al-135 in toluene. In all cases, the reactions proceeded smoothly to give the corresponding condensation products with satisfactory yields (56–75%) under extremely mild reaction conditions (Table 2). These results clearly demonstrate the superiority of Si-Al-135 catalyst support as the catalyst.

In conclusion, we found silica-alumina catalyst support an efficient catalyst for condensation reaction of 2,6-, 2,5-, and 2,4-difluoroaniline or *ortho*-halogen-aniline with 2,6-diacetylpyridine to afford the corresponding 2,6-bis(imino)pyridine in good yield. This method also offers the advantages of mild reaction conditions, using of much less solvent, and recovering and recycling of the catalyst.

Table 3 Preparation of Halogen Substituted bis(Imino)pyridine Catalyzed by Si-Al Support



^a Isolated yield.

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References

- Small, B. L.; Brookhart, M. Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.) 1998, 39, 213.
- (2) Small, B. L.; Brookhart, M.; Bennett, A. M. A. J. Am. Chem. Soc. 1998, 120, 4049.
- (3) Small, B. L.; Brookhart, M. J. Am. Chem. Soc. **1998**, *120*, 7143.
- (4) Britovsek, G. P. J.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; McTavish, S. J.; Solan, G. A.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1998**, 849.
- (5) Britovsek, G. P. J.; Bruce, M.; Gibson, V. C. B.; Kimberley, S.; Maddox, P. J.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Strömberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728.
- (6) Chen, R. F.; Qian, C. T.; Sun, J. Chin. J. Chem. 2001, 19, 866.
- (7) We applied a China patent (CN1322717A) in January 2001.
 BASF Company promulgated a WO Patent (01/07491) in February, 2001, in which two halogen substituted 2,6-

bis(imino)pyridyl iron complexes, 2,6-bis-diacetylpyridinebis(2,6-dibrom-4-methylanil)FeCl₂ and 2,6-bisdiacetyl pyridinebis(2,6-dichloroanil)FeCl₂, appeared, but there was no characterization of the complexes.

- (8) Chen, Y. F.; Qian, C. T.; Sun, J. Organometallics 2003, 22, 1231.
- (9) Sonovskikh, V. Y.; Usachev, B. I.; Röschenthaler, G. V. *Tetrahedron* 2002, 58, 1375.
- (10) Sevennard, D.; Khomotutov, O.; Koryakova, O.; Sattarova, V.; Kodess, M.; Stelten, J.; Loop, I.; Lork, E.; Pashkevich, K. I.; Röeschenthaler, G. V. *Synthesis* **2000**, 1738.
- (11) (a) Suga, K. JP 2002037841, A2, 6, 2002. (b) Kusuda, S. JP 2002146328, A2, 2002. (c) Tanaka, A.; Ohzeki, Y. Ger. Offen. DE 2835289, 1979. (d) Hiroyuki, O.; Tomoya, K.; Mitukazu, O.; Hidekazu, T. *Neltowaku Porima* 2002, 23, 11.
- (12) Grammaticakis, M. P. Bull. Soc. Chim. Fr. 1949, 761.
- (13) (a) Petrova, T. D.; Lolesnikova, I. V.; Mamatyuk, V. I.; Vetohinov, V. P.; Platonov, V. E. *Russ. Chem. B1.* **1993**, *42*, 1540. (b) Krishna, J. C.; Renuka, J.; Pooran, C.; Saroj, G. J. *Indian. Chem. Soc.* **1983**, *60*, 760. (c) Matsui, M.; Fukuyasu, K.; Shibata, K.; Muramatsu, H. J. Chem. Soc., *Perkin Trans.* 2 **1993**, *6*, 1107. (d) Kayakova, L. A.; Erzhanov, K. B.; Umarova, Z. N. J. Org. Chem. USSR (Engl. Transl.) **1988**, *24*, 111. (e) Kayaukova, L. A.; Chermova, N. V.; Manchuk, Z. N.; Erzhanov, K. B. J. Org. Chem. USSR (Engl. Transl.) **1990**, *26*, 1389. (f) Brook, G. M.; Matthews, R. S. J. Fluorine Chem. **1988**, *40*, 109. (g) Okamoto, H.; Kato, S.; Ogasawara, M.; Konnai, M.; Takematsu, T. Agric. Biol. **1991**, *55*, 2733.

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- (14) (a) Denmark, S. E.; Rivera, I. J. Org. Chem. 1994, 59, 6887.
 (b) Weingarten, H.; Chupp, J. P.; White, W. A. J. Org. Chem. 1967, 32, 3246.
- (15) The condensation reaction of 2,6-dibromoaniline with 2,6diacetylpyridine catalyzed by *p*-TsOH in refluxing toluene, with removing water by azeotropic distillation gave corresponding 2,6-bis(imino)pyridine in 58% yield if purified by recrystallization, However, it gave 30% yield when purified by flash column. See ref.⁶
- (16) (a) Kobayashi, S. Chem. Rev. 2002, 102, 2227. (b) Ma, Y.; Qian, C. T.; Wang, L.; Yang, M. J. Org. Chem. 2000, 65, 3864.
- (17) Hanamoto, T.; Sugimoto, Y.; Jin, Y. Z.; Inanaga, J. Bull. Chem. Soc. Jpn. 1997, 70, 142.
- (18) Silica-alumina catalyst support (Grade 135) was purchased from Aldrich. Si/Al = 5.62, its specific surface area is 421.3 m^2/g , average pore size 61.0545 Å. In our study, silicaalumina catalyst support (Grade 135) combined with 4 Å MS is found to be excellent catalyst for the condensation reaction of arylaldehydes with anilines, which gave almost quantitative yield.
- (19) **Typical Experimental Procedure:** Under an argon atmosphere, a mixture of 2,6-difluoroaniline (0.77 g, 6.0 mmol), 2,6-diacetylpyridine (0.41 g, 2.5 mmol), silica-alumina catalyst support (0.2 g) and molecular sieves 4 Å (0.5 g) in 8 mL toluene was stirred at 30–40 °C for 24 h. The reaction mixture was filtered and the filtration was condensed in vacuo. Anhydrous MeOH (5 mL) was added to the residue. A yellow solid was collected by filtration to yield **1a** in 65% yield. ¹H NMR (300 MHz, CDCl₃): d = 8.39 (d, 2 H, *J* = 8.0 Hz), 7.93 (t, 1 H, *J* = 7.9 Hz), 7.07 (m, 4 H,), 6.99 (t, 2 H, *J* = 7.6 Hz), 2.46 (s, 6 H). IR (KBr): n = 1636, 1576, 1465, 1369, 1277, 1237, 1215, 1126, 1032, 1002, 827, 789, 759 cm⁻¹. MS (EI): *m/z* 349 (M⁺). Anal. Calcd for $C_{21}H_{15}F_4N_3$: C, 72.19; H, 4.90; N, 12.03. Found: C, 71.88; H, 4.96; N, 11.96.
- (20) Bellabarba, R. M. et al. 20th International Conference on Organometallic Chemistry, Book of Abstract; Corfu: Greece, 2002, 230.
- (21) (a) Zeolite H-Beta Si/Al = 19.98, specific surface area 554.4 m²/g, average pore size 6.6–6.7, 5.6–5.6 Å. (b) Zeolite H-Y Si/Al = 3.35, specific surface area 739.3 m²/g, average pore size 7.4 Å, cage diameter 12 Å. (c) Si-Al(II) Si/Al = 1.0, specific surface area 240.4 m²/g.