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AN IMPROVED QUINOLINE SYNTHESIS IN THE PRESENCE OF NICKEL CHLORIDE

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Abstract – $NiCl_2 \cdot 6H_2O$ has been used as an efficient catalyst for the synthesis of quinolines by the reaction of 2-aminoaryl ketones and α-methyleneketones under the solvent-free conditions. The clean, mild acidity conditions and quantitative yields of products are attractive features of this reaction which build a suitable method for sensitive substrates, particularly in drug synthesis.

INTRODUCTION

The quinoline nucleus occurs in several natural compounds (Cinchona alkaloids) and pharmacologically active substances displaying a broad range of biological activity.[1] The biological activity of quinoline compounds has been found to possess antiasthmatic,[2] antibacterial,[3] anti-inflammatory[4] and antihypertensive properties.[5] In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes.[6] The Friedländer reaction is a well-known method for preparing quinolines and polypyridyl bridging ligands,[7] it is still considered as one of the most useful methods for preparing quinolines and related bicyclic azaaromatic compounds. Classically, the process consists of an acid or base catalyzed condensation followed by a cyclodehydration between a 2-aminoaryl ketone and a carbonyl compound possessing a reactive α-methylene group. The Friedländer reaction is carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of base or by heating a mixture of the reactants at high temperature ranging from 150 to 220 ºC in the absence of catalysts.[8] Under thermal or base catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-keto esters.[9] Subsequent work showed that acid catalysts are more effective than base catalysts for the Friedländer annulation. Protic acids[10] as well as Lewis acids[11] are known to promote these reactions. However, most of the methods have significant drawbacks such as low yields of the products, harsh reaction conditions, difficulties in workup, and use of stoichiometric quantities of reagents. Since quinoline derivatives are increasingly useful and important in

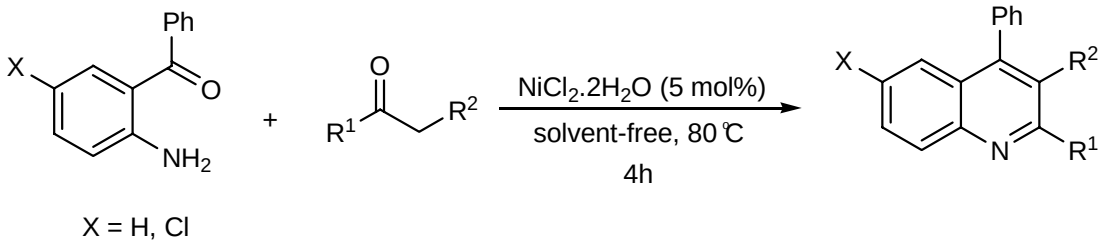
drugs and pharmaceuticals, the development of a simple, efficient, and environmentally benign protocol is still desirable.

Recently, $NiCl_2 \cdot 6H_2O$ was shown to be an effective promoter for the Biginelli three-component condensation reaction.[12] It has also been reported as a mild useful and inexpensive Lewis acid catalyst for the synthesis of α-aminonitriles,[13a] formal hydrochromination of alkynes,[13b] and 2,4,5-triarylimidazoles.[13c]

RESULTS AND DISCUSSION

In continuation of our interest in synthesis of heterocyclic compounds using heterogeneous catalyst and Lewis acids,[14] here in we report a new catalytic method for the synthesis of poly substituted quinolines in the presence of $NiCl_2 \cdot 6H_2O$.

At first we studied the efficacy of our catalyst in a model reaction between 2-aminoenzophenone, and ethyl acetoacetate under solvent-free conditions at 80 ºC. It was found that the best results were obtained using 5 mol% of catalyst. Intrigued by the results obtained, substituted quinolines were prepared from different 2-aminoaryl ketones and various α-methyleneketones (Scheme 1).



Scheme 1

2-Aminoaryl ketones included 2-aminobenzophenone derivatives while the α-methyleneketones included cycloalkanones, 1,3-diketones (cyclic and acyclic) and β-keto esters (Table 1). The quinolines were formed in high yields (88-95%) within 4 h. The method showed the compatibility with different functional groups such as alkyl, acyl, halogen and alkoxycarbonyl. The catalyst, $NiCl_2 \cdot 6H_2O$ is commercially available, inexpensive and nonhazardous. To illustrate the need of catalyst, $NiCl_2.6H_2O$, for this reaction, experiments were conducted in which the reaction of 2-aminoenzophenone, and ethyl acetoacetate was studied in the absence of catalyst. The reaction was not completed even after 24 h.

In conclusion, the present work describes an efficient new methodology for the synthesis of a class of poly substituted quinolines by one-pot reaction of 2-aminoaryl ketones and various α-methyleneketones. The cheapness and availability of the reagents, easy and clean work-up procedure and good yields make the method attractive for the synthesis of various quinolines.

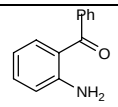
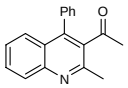
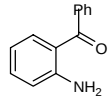
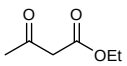
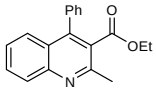
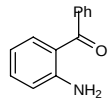
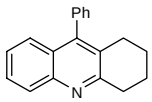
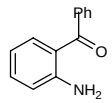
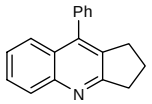
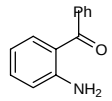
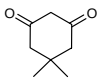
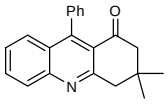
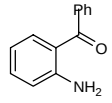
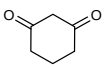
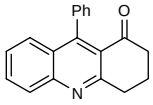
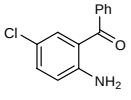
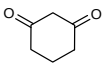
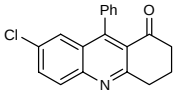
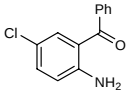
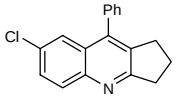
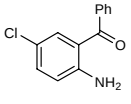
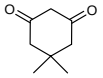
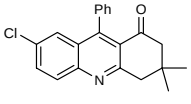
EXPERIMENTAL

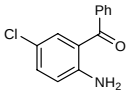
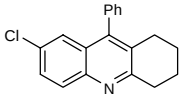
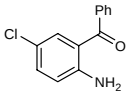
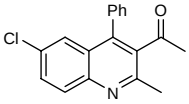
Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz.

General Procedure

A mixture of 2-aminoaryl ketone (1.0 mmol), α-methyleneketone (1.1 mmol) and $NiCl_2 \cdot 6H_2O$ (0.05 mmol) was heated under solvent-free conditions with stirring at 80°C for 4 h. After completion of the reaction as indicated by TLC (eluent: *n*-hexane/EtOAc: 2/1) the reaction mixture was washed with H_2O (2×10 mL), and filtered. Finally the crude solid product was recrystallized from EtOH.

Table 1: Synthesis of quinolines in the presence of $NiCl_2.2H_2O$ under solvent-free conditions at 80°C in 4 h.

Entry	2-Aminoaryl ketone	CH-acid	Product	Yield (%)[a]	Mp (°C)	
					Found	Reported[b]
1				90	111-112	110-111[10f]
2				91	100-101	99-100[10f]
3				94	156-157	155-156[10f]
4				90	130-132	130-131[10f]
5				89	190-192	190-191[10f]
6				92	155-156	156-157[10f]
7				89	185-186	185-186[9]
8				88	106-107	107-109[9]
9				92	208-209	209-210[10f]

10				95	164-165	165-166[10f]
11				91	150-151	152-153[9]

[a] Isolated yield.

[b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the procedures given in the references.

ACKNOWLEDGEMENTS

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REFERENCES

1. (a) M. P. Maguire, K. R. Sheets, K. M. Vety, A. P. Spada, and A. Zilberstein, *J. Med. Chem.*, 1994, **37**, 2129. (b) G. Roma, M. D. Braccio, G. Grossi, F. Mattioli, and M. Ghia, *Eur. J. Med. Chem.*, 2000, **35**, 1021. (c) Y.–L. Chen, K.–C. Fang, J.–Y. Sheu, S. L. Hsu, and C.–C. Tzeng, *J. Med. Chem.*, 2001, **44**, 2374.
2. (a) R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R.Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang, and R. J. Zamboni, *J. Org. Chem*., 1996, **61**, 3398. (b) M. E. Zwaagstra, H. Timmerman, A. C. van de Stolpe, F. J. de Kanter, M. Tamura, Y. Wada, and M. Q. Zhang, *J. Med. Chem.*, 1998, **41**, 1428.
3. (a) K. Mogilaiah, D. S. Chowdary, and R. B. Rao, *Ind. J. Chem.*, 2001, **40B**, 43. (b) Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu, and C. C. Tzeng, *J. Med. Chem.*, 2001, **44**, 2374.
4. (a) G. Roma, M. D. Braccio, G. Grossi, F. Mattioli, and M. Ghia, *Eur. J. Med. Chem.*, 2000, **35**, 1021. (b) B. Kalluraya and S. Sreenizasa, *Farmaco*, 1998, **53**, 399.
5. (a) Y. Morizawa, T. Okazoe, S. Z. Wang, J. Sasaki, H. Ebisu, M. Nishikawa, and H. Shinyama, *J. Fluor. Chem.*, 2001, **109**, 83. (b) P. L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, R. Greco, C. Manera, A. Martinelli, P. Nieri, and G. Saccomanni, *Eur. J. Chem.*, 2000, **35**, 815.
6. (a) I. Saito, S. Sando, and K. Nakatani, *Bioorg. Med. Chem.*, 2001, **9**, 2381. (b) K. Nakatani, S. Sando, and I. Saito, *J. Am. Chem. Soc.*, 2000, **122**, 2172. (c) C. H. Nguyen, C. Marchand, S. Delage, J. S. Sun, T. Garestier, H. Claude, and E. Bisagni, *J. Am. Chem. Soc.*, 1998, **120**, 2501.
7. V. V. Kouznetsov, L. Y. V. Méndez, and C. M. M. Gómez, *Curr. Org. Chem.*, 2005, **9**, 141.
8. (a) C. C. Cheng and S. J. Yan, *Org. React.*, 1982, **28**, 37. (b) R. P. Thummel, *Synlett*, 1992, 1. (c) H. Eckert, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 208. (d) S. Gladiali, G. Chelucci, M. S. Mudadu, M.

A. Gastaut, and R. P. Thummel, *J. Org. Chem.*, 2001, **66**, 400.

9. E. A. Fehnel, *J. Org. Chem.*, 1966, **31**, 2899.
10. (a) D. R. Sliskovic, J. A. Picard, W. H. Roark, B. D. Roth, E. Ferguson, B. R. Krause, R. S. Newton, C. Sekerke, and M. K. Shaw, *J. Med. Chem.*, 1991, **34**, 367. (b) M. Dabiri, M. Baghbanzadeh, M. S. Nikcheh, and Y. Vakilzadeh, *Monatsh. Chem.*, 2007, **138**, DOI: 10.1007/s00706-007-0712-4. (c) M. Suzuki, H. Iwasaki, Y. Fujikawa, M. Kitahara, M. Sakashita, and R. Sakoda, *Bioorg. Med. Chem.*, 2001, **9**, 2727. (d) S. J. Song, S. J. Cho, D. K. Park, T. W. Kwon, and S. A. Jenekhe, *Tetrahedron Lett.*, 2003, **44**, 255. (e) J. S. Yadav, P. P. Rao, D. Sreenu, S. S. Rao, V. N. Kumar, K. Nagaiah, and A. R. Prasad, *Tetrahedron Lett.*, 2005, **46**, 7249. (f) A. Shaabani, E. Soleimani, and A. Badri, *Synth. Commun.*, 2007, **37**, 629.
11. (a) B. R. McNaughton and B. L. Miller, *Org. Lett.* 2003, **5**, 4257. (b) J. S. Yadav, B. V. S. Reddy, and K. Premalatha, *Synlett*, 2004, 963. (c) J. Wang, X. Fan, X. Zhang, and L. Han, *Can. J. Chem.*, 2004, **82**, 1192. (d) P. Arumugam, G. Karthikeyan, R. Atchudan, D. Muralidharan, and P. T. Perumal, *Chem. Lett.*, 2005, **34**, 314. (e) S. K. De and R. A. Gibbs, *Tetrahedron Lett.*, 2005, **46**, 1647. (f) J. Wu, L. Zhang, and T. N. Diao, *Synlett*, 2005, 2653.
12. (a) J. Lu and H. Ma, *Synlett*, 2000, 63. (b) J. Lu, and Y. Bai, *Synthesis*, 2002, 466.
13. (a) S. K. De, *J. Mol. Catal. A: Chem.*, 2005, **225**, 169. (b) K. Takai, S. Sakamoto, T. Isshiki, and T. Kokumai, *Tetrahedron*, 2006, **62**, 7534. (c) M. M. Heravi, K. Bakhtiari, H. A. Oskooie, and S. Taheri, *J. Mol. Catal. A: Chem.*, 2007, **263**, 279.
14. (a) M. Dabiri, P. Salehi, A. A. Mohammadi, and M. Baghbanzadeh, *Synth. Commun.*, 2005, **35**, 279. (b) P. Salehi, M. Dabiri, M. Baghbanzadeh, and M. Bahramnejad, *Synth. Commun.*, 2006, **36**, 2287. (c) M. Dabiri, P. Salehi, A. A. Mohammadi, M. Baghbanzadeh, and G. Kozehgiry, *J. Chem. Res.*,(*S*) 2004, 570. (d) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh *Heterocycles*, 2005, **65**, 1177. (e) M. Dabiri, M. Baghbanzadeh, S. Kiani, and Y. Vakilzaeh, *Monatsh. Chem.*, 2007, **138**, 997. (f) M. Dabiri, P. Salehi, M. Baghbanzadeh, and M. Bahramnejad, *Tetrahdron Lett.*, 2006, **47**, 6983. (g) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh, *Synlett*, 2005, 1155. (h) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh, *Tetrahedron Lett.*, 2005, **46**, 7051. (i) P. Salehi, M. Dabiri, M. A. Zolfigol, S. Otokesh, and M. Baghbanzadeh, *Tetrahedron Lett.*, 2006, **47**, 2557. (j) M. Dabiri, P. Salehi, M. A. Zolfigol, and M. Baghbanzadeh, *Heterocycles*, 2007, **71**, 677. (k) M. Dabiri, P. Salehi, M. Baghbanzadeh, M.A. Zolfigol, and M. Bahramnejad, *Synth. Commun.*, 2007, **37**, 1201. (l) M. Dabiri, P. Salehi, M. Baghbanzadeh, Y. Vakilzadeh, and S. Kiani, *Monatsh. Chem.*, 2007, **138**, 595. (m) M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary, and A. A. Mohammadi, *Tetrahedron Lett.*, 2005, **46**, 6123. (n) M. Baghbanzadeh, P. Salehi, M. Dabiri, and G. Kozehgary, *Synthesis*, 2006, 344.