Efficient procedure for the synthesis of quinoline derivatives by NbCl$_5$.PEG and NbCl$_5$ in glycerol as green solvent

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Abstract

Quinolines, an important class of potentially bioactive compounds, have been synthesized by treatment of *O*-aminoarylketones and carbonyl compounds utilizing niobium-(V) chloride /-polyethylenglycole(NbCl$_5$.PEG) and niobium(V) chloride (NbCl$_5$) as available and inexpensive catalysts. The quinoline derivatives were prepared in glycerol, as an excellent solvent in terms of environmental impact, with high yields (76-98%) and short reaction times (15-90 min).

Keywords: Quinoline; niobium-(v) chloride; glycerol; green solvent; solid acid.

Introduction

The synthesis of quinolines has been of considerable interest to chemists because these oxygen-containing heterocycles may contribute to potential anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory and anti-platelet properties [1- 3]. Various methods have been reported for the synthesis of quinolines including the Skraup [4], Conrad–Limpach–Knorr [5], Pfitzinger [6], Friedlander [7], and Combes [8]. However, the Friedlander condensation is still considered as a popular method for the synthesis of quinoline derivatives [9-14]. In this method, *O*-aminobenzophenone condenses with ketones or -diketones to yield quinolines.

Solvents are chemical substances used in huge amounts for many different applications. One of the key areas of "Green

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Chemistry" is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents. Glycerol, which is a non-toxic, biodegradable liquid which is manufactured from renewable sources, shows similar properties as an ionic liquid and has a high potential to serve as green solvent for organic syntheses. It has a very high boiling point and negligible vapor pressure; it is compatible with most organic and inorganic compounds, and does not require special handling or storage. Glycerol permits to turn to the advantages of both water (low toxicity, low price, large availability, renewability) and ionic liquids (high boiling point, low vapor pressure) [15].

The oxophilicity of high valence Nb(V) in niobium(v)chloride has enabled it to act as the reagent/catalyst for several Lewis acid-mediated reactions such as the intramolecular oxidation–reduction process [16], the Diels–Alder reaction [17], allylation of aldehydes and imines [18] and complex formations [19].

Nevertheless, the development of new synthetic methods for the efficient preparation of heterocycles containing quinoline fragment is an interesting challenge. Therefore, in this report, we describe synthesis of quinoline deriveatives

by treatment of 2-aminobenzophenone with various carbonyl compounds using $NbCl_5.PEG$ and $NbCl_5$ as available catalysts in glycerol with high yields.

Experimental

General

Carbonyl compounds and *O*-aminobenzophenone were purchased from Merck Chemical Company. Purity determinations of the products were accomplished by TLC on silica-gel polygram SILG/UV 254 plates. Melting points were determined by an electrothermal 9100 system open capillaries and were uncorrected. IR spectra were taken on a perkin Elmer 781 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX 250 and 62.9 MHz spectrometer in $CDCl_3$ with chemical shift given in ppm relative to TMS as internal standard. Mass spectra were measured on a shimadzu GC-Ms-QP5050 mass spectrometer.

Preparation of NbCl_5.PEG:

The catalyst was prepared by stirring a mixture of $NbCl_5$ (0.56 gr) and polyethylenglycole (0.44 g) in 5 mL of CH_2Cl_2 for 5 h at room temperature. The solution was concentrated under vacuum and diethyl ether (5 mL) was added. The precipitate was filtered and washed with

ether. The obtained solid (56% $NbCl_5$.PEG) was dried at ambient temperature for 2 h and then stored in a dry container.

General procedure for the preparation of quinoline derivatives by NbCl₅ (method 1)

$NbCl_5$ (0.1 mmol) in glycerol (2 mL) was added to a mixture of carbonyl compounds (1 mmol) and 2-amino-5-chlorobenzophenone or 2-aminobenzophenone (1 mmol). The mixture was stirred at 110 ^{0}C for appropriated reaction time (Table 3). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was quenched by the addition of saturated aq. $NaHCO_3$ solution and the reaction mixture was filtered and washed with ethanol. The crude solid product was crystallized from EtOH to afford the pure product.

General procedure for the preparation of quinoline derivatives by NbCl₅.PEG (method 2)

0.1 gr of $NbCl_5$.PEG was added to a mixture of carbonyl compounds (1 mmol) and 2-amino-5-chlorobenzophenone or 2-aminobenzophenone (1 mmol). The mixture was stirred at 110 ^{0}C for appropriated reaction time (Table 3). The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the product was dissolved to

ether and filtered to recover the catalyst. The solvent was evaporated and the crude product recrystallized from ethanol. The crude solid product was crystallized from EtOH to afford the pure product and characterized by ^{1}H NMR, ^{13}C NMR, IR and MS spectroscopy analysis.

3b: 7-Chloro-9-phenyl-3,4-dihydro-1-2H-acridinone: Yellow solid, m.p. 184 ^{0}C (Lit. [20] 185 ^{0}C); ^{1}H NMR (250 MHz, $CDCl_3$): 2.26 (q, 2H, J= 6.4 Hz), 2.72 (t, 2H, J= 6.4 Hz), 3.37 (t, 2H, J= 6.4 Hz), 7.17 (t, 2H), 7.42 (s, 1H), 7.53 (m, 3H), 7.69 (d, 1H, J= 8.8 Hz), 8.01 (d, 1H, J= 8.8 Hz); IR (KBr, cm^{-1}) 3024, 2975, 2870, 1698, 1549, 1476, 1380, 1210, 1075, 1007, 970, 838, 697; MS (m/z, %): 308((M+2)-1, 34), 306 (M-1, 100), 281(5), 280 (29), 278(15), 253(4), 244(10), 215(27), 188(12) , 153(17), 120(20), 107(15).

3f: Methyl-6-chloro-2-methyl-4-phenyl-3-quinolinecarboxylat:Yellow solid, m.p. 135 ^{0}C, (Lit. [20] 135 ^{0}C); ^{1}H NMR (250 MHz, $CDCl_3$): 2.74 (s, 3H), 3.56 (s, 3H), 7.25–8.01 (c, 8H). ^{13}C NMR (62.9 MHz, $CDCl_3$) 23.7, 52.2, 125.2, 125.8, 128.0, 128.5, 128.8, 129.1, 130.5, 131.2, 132.4, 134.9, 145.5, 146.1, 145.9, 154.9, 168.6; IR (KBr , cm^{-1}) 3035, 2958, 2900, 1749, 1561, 1455, 1402, 1297, 1237, 1182, 1070, 872, 767; MS (m/z, %): 313(M+2, 31), 311(M^+, 100), 296(6),

281(50), 279(97), 254(14), 251(16), 236(4), 211(10), 189(34), 175(52), 108(37), 94(33), 74(17).

3n: 2-Chloro-11-phenyl-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolone:

Yellow solid, m.p. 195 ^{0}C (Lit. [21] 195 ^{0}C); ^{1}H NMR (250 MHz, CDCl$_3$): 1.60 (s, 2H), 1.84 (s, 4H), 2.68 (m, 2H) 3.26 (m, 2H), 7.22- 7.96 (m, 8H); ^{13}C NMR (62.9 MHz, CDCl$_3$) 26.9, 28.4, 30.7, 31.8, 40.1, 125.1, 127.7, 127.9, 128.6, 129.0, 129.3, 130.3, 131.3, 134.8, 136.9, 144.2, 144.7, 165.1; IR (KBr, cm^{-1}) 3080, 3050, 2930, 2850, 1615, 1600, 1500, 1470, 1360, 1180, 990, 870, 820, 680; MS (m/z, %): 308((M+2)-1, 33), 306(M-1, 100), 292(9), 280 (15), 277(12), 252(13), 242(17), 228(18), 215(18) ,201(10), 188(10), 127(23), 120(25), 107(15).

3r: 6-Chloro-2,4-diphenylquinoline: Yellow solid m.p: 206 °C, (Lit. [21] 208 ^{0}C); ^{1}H NMR (250 MHz, CDCl$_3$): 7.25-8.19 (m, 14H); ^{13}C NMR (62.9 MHz, CDCl$_3$) 120.5, 124.5, 126.5, 127.5, 128.7, 128.8, 128.9, 129.4, 129.6, 130.4, 131.7, 132.2, 137.5, 139.2, 147.2, 148.4, 157.1; IR (KBr, cm^{-1}): 3019, 2985, 1580, 1508, 1465, 1355, 1150, 1005, 840, 790, 755; MS (m/z, %): 316(M +2, 43), 314(M$^+$, 100), 280(27), 277(18), 250(6), 236(7), 201(17), 175(13), 139(57), 125(19).

Results and discussion

Due to the pharmacological properties of quinolines, development of synthetic methods and easy access to these compounds are desirable. Therefore, in this paper, we report synthesis of quinoline deriveatives in the presence of NbCl$_5$.PEG and NbCl$_5$ as inexpensive and available catalysts. In order to evaluate the catalytic efficiency of NbCl$_5$ and to determine the most appropriate reaction conditions, initially, a model study was carried out on the synthesis of quinoline **3** (Scheme 1) by the condensation of 2-aminobenzophenone **1** and 1,3-cyclohexadione **2** in different reaction conditions.
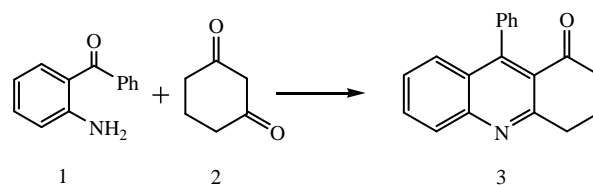
Scheme 1.

In preliminary experiment, this reaction was carried out in various solvents, with NbCl$_5$ (0.1 mmol) as- catalyst (Table 1). The reaction was proceeded perfectly in polar solvents (Table 1, Entries 7-16), but the yields decreased when the reaction was carried out in nonpolar solvents (Table 1, entries 3-6). It was very surprising that the reaction was preceded in excellent yields (98%) in glycerol medium (Table 1, Entry

16). The reaction could be carried out under solvent-free condition and in low yield (Table 1, Entries 1 and 2).

Table 1. The effect of various solvents in the reaction 2-amino-benzophenone (1 mmol), 1,3-cyclohexadione (1 mmol), catalyst (0.1 mmol), and solvent (2 mL)

Entry	Solvent/condition	Yield (%)	Entry	Solvent/condition	Yield (%)
1	Solvent-free (80 ^{o}C)	35	9	1,2-Dichloroethane (r.t.)	55
2	Solvent-free (100 ^{o}C)	58	10	1,2-Dichloroethane (80 ^{o}C)	68
3	n-Hexane (r.t.)	15	11	EtOH (r.t.)	52
4	CH_2Cl_2 (r.t.)	20	12	EtOH (80 ^{o}C)	63
5	$CHCl_3$ (r.t.)	45	13	MeOH (r.t.)	82
6	THF (r.t.)	48	14	Glycerol (80 ^{o}C)	83
7	CH_3CN (r.t.)	60	15	Glycerol (100 ^{o}C)	95
8	CH_3CN (80 ^{o}C)	76	16	Glycerol (110 ^{o}C)	98

To obtain the optimized reaction conditions, the amount of catalyst was also changed. The results are summarized in Table 2. Consequently, among the tested amounts, the condensation of 2-aminobenzophenone and 1,3-cyclohexadione was best catalyzed by 0.1 mmol of $NbCl_5$ in glycerol at 110 ^{o}C. Control experiments indicate that in the absence of the catalyst, the reaction at the same condition gives quinoline in a rather low yield of 33% (Table 2, Entry 1).

To determine the optimum quantity of $NbCl_5$.PEG in reaction of 2-amino-benzophenone and 1,3- cyclohexadione, different amounts of $NbCl_5$.PEG were used in various solvents. The best conditions of corresponding catalyst were obtained 0.1 g under solvent free conditions.

To establish the generality and applicability of this method, 2-amino-5-chlorobenzophenone/ 2-aminobenzophenone and carbonyl compounds were subjected to the same reaction condition to furnish the corresponding quinolines in good to excellent yields (Scheme 2, Table 3).

Not only diketones (Table 3, Entries 1–11) but also ketones (Table 3, Entries 12-–17) afforded the desired products in good to excellent yields (76-90%) in short reaction time (40–75 min). It is delighted that the reaction time of 1,3-diphenyl propane-1,3-

dione was longer than those of acethylaceton, which is probably due to low reactivity of carbonyl groups. Also, the reaction time of 2-amino-5-chlorobenzophenone and dicarbonyl compounds was longer than those of 2-aminobenzophenone. The reaction of cyclic diketones took place faster than open chain analogues.
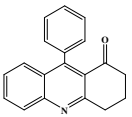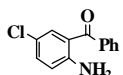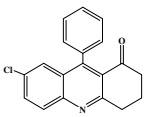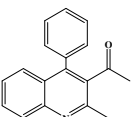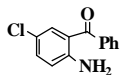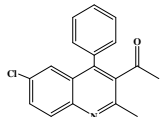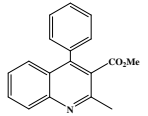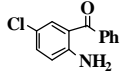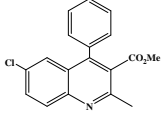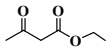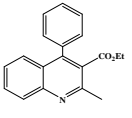
Table 2. Effect of temperature and catalyst amount on the synthesis of 2- quinoline derivatives *via* a condensation of 2-aminobenzophenone and 1,3- cyclohexadione in the presence of $NbCl_5$ in glycerol
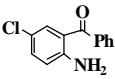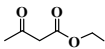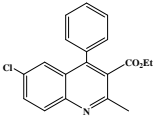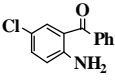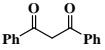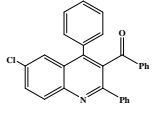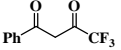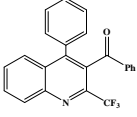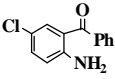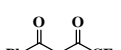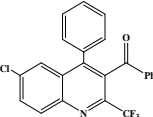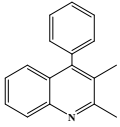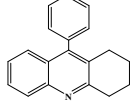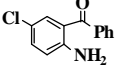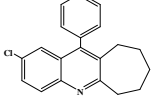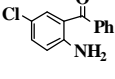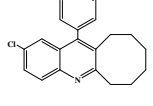
Entry	Catalyst (mmol)	Yield (%)			
		r.t.	60 ^{0}C	80 ^{0}C	110 ^{0}C
1	None	-	10	15	33
2	0.01	15	20	25	52
3	0.05	25	40	56	78
4	0.1	55	76	88	98
5	0.2	60	78	90	98
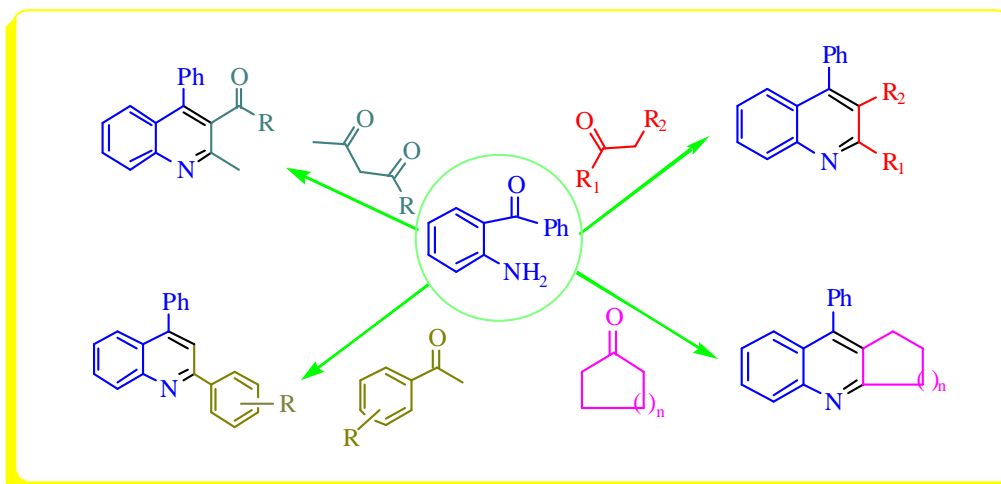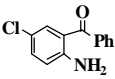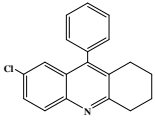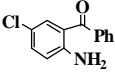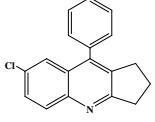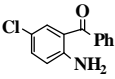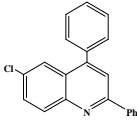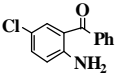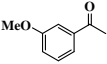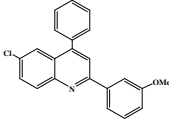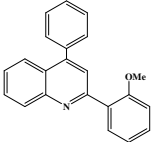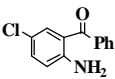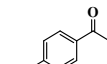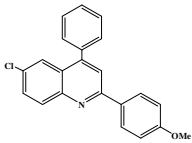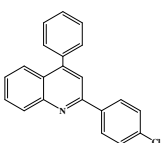
Scheme 2.

Table 3. Synthesis of quinolines catalyzed by NbCl$_5$.PEG and NbCl$_5$

Entry	Substrate 1	Substrate 2	Quinoline 3	Method 1		Method 2	
				time (min)	Yield (%)[a]	time (min)	Yield (%)[b]
1	1a	2a	3a	15	95	15	92
2	1b	2a	3b	20	98	15	95
3	1a	2b	3c	25	93	30	95
4	1b	2b	3d	35	95	30	98
5	1a	2c	3e	50	87	30	76
6	1b	2c	3f	60	78	30	80
7	1a	2d	3g	45	82	30	76

8	1b	2d	3h	50	85	30	78
9	1b	2e	3i	70	80	50	76
10	1a	2f	3j	60	78	50	80
11	1b	2f	3k	45	84	50	85
12	1a	2g	3l	75	81	50	83
13	1a	2h	3m	50	79	50	85
14	1b	2i	3n	40	85	50	82
15	1b	2j	3o	55	82	50	78

16	1b	2h	3p	45	89	50	92
17	1b	2k	3q	45	90	50	90
18	1b	2l	3r	90	84	90	86
19	1b	2m	3s	90	88	90	92
20	1a	2n	3t	90	86	90	86
21	1b	2o	3u	90	91	90	95
22	1a	2p	3v	90	79	90	83
23	1a	2s	3w	90	76	90	83
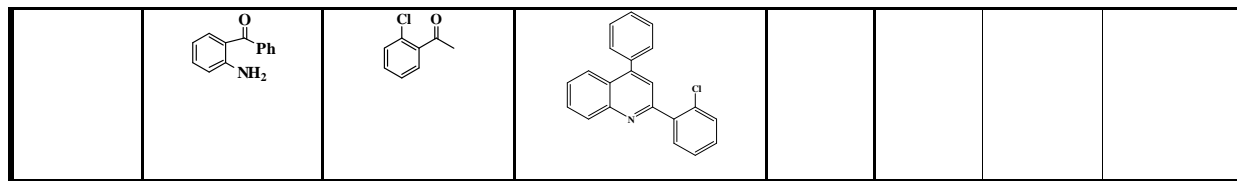
	(structure: O, Ph, NH₂)	(structure: Cl, O)	(structure: quinoline with Ph and Cl)				

[a]reaaction conditions: carbonyl compounds (1 mmol), 2-amino-5-chlorobenzophenone or 2-amino benzophenone (1 mmol), NbCl$_5$ (0.1 mmol) and glycerol (2 mL); reactions conducted at 110 ^{0}C.

[b]reaaction conditions: carbonyl compounds (1mmol), 2-amino-5-chlorobenzophenone or 2-amino benzophenone (1 mmol), NbCl$_5$.PEG (0.1 g-); reactions conducted at 110 ^{0}C.

These reactions also were preceded with acetophenone derivatives (Table 3, Entries 18-23). In these cases, the reaction times are longer. It may be due to the less activity of acetophenone derivatives than dicarbonyl compounds. All the aforementioned reactions (Table 3) delivered good product yields and accommodated a wide range of aromatic carbonyl compound bearing both electron-donating and electron-withdrawing substituents. The reactivity of different aromatic carbonyl compounds was influenced by the nature and position of the substituents on the aromatic ring. The aromatic carbonyl derivatives having an electron-donating substituent were highly reactive and gave the products in excellent yields (Entries 19-21). When the aromatic carbonyl compounds contained electron-withdrawing group, the reaction yield was decreased (Entries 22 and 23).

A reasonable pathway for the reaction of *o*-amino benzophenone with carbonyl compounds conducted in the presence of NbCl$_5$ is presented by Scheme 3. The first step involves the formation of activated benzophenone by NbCl$_5$ followed by its reaction with carbonyl compound that subsequently undergoes elimination reaction to produce the compound intermediate. The intermediate undergoes further elimination reaction to afford heterocycle of quinoline.

In Table 4, the efficiency of our method for the synthesis of quinoline from *o*-amino benzophenone and carbonyl compound is compared with some other published works in the literature. Each of these methods have their own advantages, but they often suffer from some troubles including the use of organic solvent (Entry 5), long reaction time (Entries 3-7) and employ of non-recyclable catalyst (Entry 4).

It is noteworthy to mention that NbCl$_5$.PEG is recyclable catalyst and could be reused. It could be recovered by filtration and washing with diethyl ether. The recycled catalyst was reused in the model reaction.

The results of the first experiment and the subsequent were almost consistent in yield after five runs (Table 5).
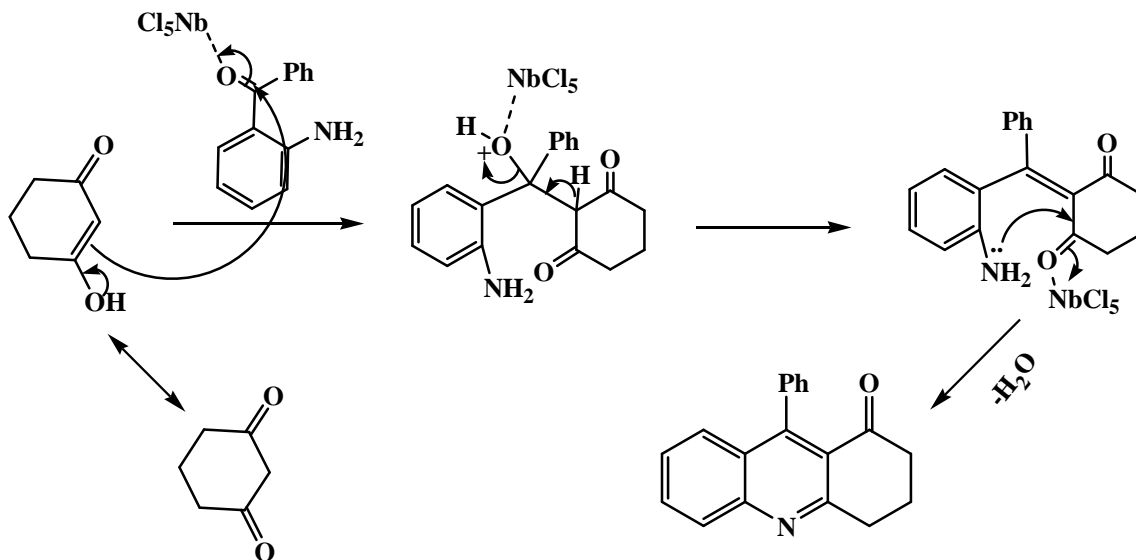
Scheme 2. The proposed mechanism for the synthesis of quinolines by NbCl₅

Table 4. One-pot condensation of *o*-amino benzophenone, 1,3-cyclohexanone in the presence of different catalysts

Run	Catalyst	Condition	Solvent	Time (h)	Yield (%)	Ref
1	NbCl₅	110 ^{0}C	Glycerol	15 (min)	95	-
2	NbCl₅.PEG	110 ^{0}C	-	15 (min)	92	-
3	Ag₃PW₁₂O₄₀	Reflux	EtOH	3.5	87	22
4	HCl	100-200 ^{0}C	H₂O	1	68	23
5	HClO₄/SiO₂	Reflux	CH₃CN	3	92	24
6	Zr(HSO₄)₄	Reflux	H₂O	13	87	25
7	bmimCl-ZnCl₂	r.t	Ionic Liquid	24	80	26

Table 5. Recyclability of NbCl$_5$.PEG as catalyst in synthesis of quinolines[a]

Entry	Cycle	Yield (%)[b]
1	0	92
2	1	92
3	2	88
4	3	85
5	4	83
6	5	78

[a]reaaction conditions: 1,3-cyclohexadione (1 mmol), 2-aminobenzophenone (1 mmol), NbCl$_5$.PEG (0.1 g); reactions conducted for 15 min at 110 ^{0}C.

[b]The yield refers to pure isolated product.

Conclusion

In conclusion, efficient synthesis of quinoline derivatives has been achieved by a one-pot coupling reaction of carbonyl compounds and *O*-aminobenzophenone using catalytic amounts of NbCl$_5$ in glycerol. Simple reaction procedures, inexpensive catalysts and single product formation make the method an attractive protocol over the existing procedures.

Acknowledgments

References

[1] M.P. Maguire, K.R. Sheets, K. McVety, A.P. Spada, A.J. Zilberstein. *Med. Chem.,* **1994**, *37,* 2129-2137.

[2] A.V. Malkov, M.A. Kabeshov, M. Bella, O. Kysilka, D.A. Malyshev, K. Pluhackova, P. Kocovsky, *Org. Lett.,* **2007***, 9*, 5473-5476.

[3] M.A.E. Shaban, M.A.M. Taha, E.M. Sharshira*, Adv. Heterocycl.Chem.,* **1991***,* 52, 1-153.

[4] G.D. Yadav, P.K. Rahul, H. Saumydeep. *International Review of Chemical Engineering.*, **2012**, *4*, 597-607.

[5] N.D. Heindel, T.A. Brodof, J.E. Kogelschatz, *J Heterocycl. Chem*., **1966***, 3,* 222-223.

[6] W. Pfitzinger*, J Prakt. Chem.,* **1886***, 33,* 100-100.

[7] a) E.A. Fehnel, *J. Org. Chem.,* **1966**, *31*, 2899-2902; b) A. Bañón-Caballero, G. Guillena, C. Nájera, *J. Org. Chem.*, **2013**, *78*, 5349-5356; c) J. Marco-Contelles, E. Pe´rez-Mayoral, A. Samadi, M. Carmo Carreiras, E. Soriano. *Chem. Rev.,* **2009**, *109,* 2652-2671; d) Q. Shen, L. Wang, J. Yu, M. Liu, J. Qiu,

L. Fang, F. Guo, J. Tang, *Synthesis*, 2012, *44*, 389-392.

[8] E. Roberts, E.E. Turner, *J. Chem. Soc.,* **1927**, 1832-1857.

[9] J.S. Yadav, P.P. Rao, D. Sreenu, R.S. Rao, V.Kumar, K. Nagaiah, A.R. Prasad, *Tetrahedron Lett.,* **2005**, *46,* 7249-7253.

[10] J. Wu, H. G. Xia, K. Gao, *Org. Biomol. Chem.,* **2006**, *4*, 126-129.

[11] A. Arcadi, M. Chiarini, S.D. Giuseppe, F. Marinelli, *Synlett.,* **2003**, *2,* 203-206.

[12] M. Zhu, W. Fu, C. Xun, G. Zou, *Bull. Korean Chem. Soc.,* **2012**, *33*, 43-47.

[13] S.J. Song, S.J. Cho, D.K. Park, T.W. Kwon, S.A. Jenekhe, *Tetrahedron Lett.,* **2003**, *44*, 255-257.

[14] S.A. Palimkar, S.A. Siddiqui, T. Daniel, R.J. Lahoti, K.V. Srinivasan, *J. Org. Chem.,* **2003**, *68*, 9371-9378.

[15] A. Wolfson, C. Dlugy, Y. Shotland, *Environ Chem. Lett.,* **2007**, *5*, 67-71.

[16] K. Suzuki, T. Hashimoto, H. Maeta, T. Matsumoto, *Synlett.,* **1992**, 125-128.

[17] J. Howarth, K. Gillespie, *Tetrahedron Lett.,* **1996**, *37*, 6011-6012.

[18] C. Kleber, Z. Andrade, G.R. Oliveira. *Tetrahedron Lett.,* **2002**, *43,* 1935-1937.

[19] M. Aresta, A. Dibenedetto, P. Stufano, B. Maria Aresta, S. Maggi, I. Papai, T.A. Rokob, B. Gabriele. *Dalton Trans.*, **2010**, *39*, 6985.

[20] M.A. Zolfigol, P. Salehi, A. Ghaderi, M. Shiri, Z. Tanbakouchian, *Journal of Molecular Catalysis A: Chemical.*, **2006**, *259*, 253-258.

[21] C. Gisela, M. Mariela, P. Juan, M. Bruno. *Tetrahedron Letters.*, **2006**, *47,* 8811-8815.

[22] J.S. Yadav, B.V.S. Reddy, P. Sreedhar, R. SrinivasaRao, K. Nagaiah, *Synlett.*, **2004**, 2381-2385.

[23] G. Kempter, P.Z. Klug. *Chem.*, **1971**, 61, 3916-3919.

[24] M. Narasimhulu, T. Srikanth Reddy, K.Chinni Mahesh, P. Prabhakar, C. Bhujanga Rao, Y. Venkateswarlu. *J. Mol. Catal. A: Chem.*, **2007**, *266,* 114-117.

[25] M.A. Zolfigol, P. Salehi, A. Ghaderi, M. Shiri. *Catal.Commun.*, **2007**, *8,* 1214-1218.

[26] G. Karthikeyan, P.T. Perumal. *J. Heterocyclic Chem.*, **2004**, *41,* 1039-1041.