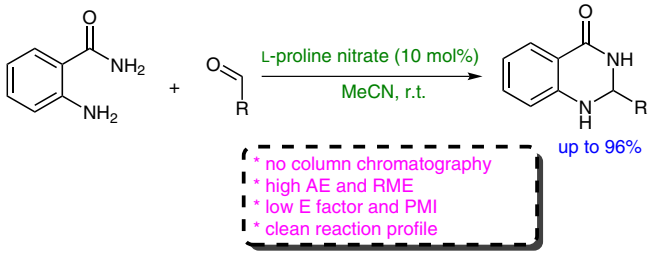
Synlett S. P. Bahekar et al. Letter

Efficient Access to 2,3-Dihydroquinazolin-4(1*H*)-ones by Environmentally Benign L-Proline Nitrate as Recyclable Catalyst

Sandeep P. Bahekar
Nityanand D. Dahake
Prashant B. Sarode
Hemant S. Chandak*

Department of Chemistry, G. S. Science, Arts and Commerce College, Khamgaon 444303, India
chemants@gmail.com



Received: 10.07.2015
Accepted after revision: 24.08.2015
Published online: 15.09.2015
DOI: 10.1055/s-0035-1560483; Art ID: st-2015-d0532-l

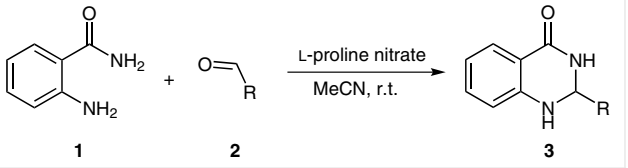
Abstract An L-proline nitrate assisted protocol is described for the construction of 2,3-dihydroquinazolin-4(1*H*)-ones. The catalyst can be recovered easily and is reusable for at least six cycles without significant loss of catalytic efficiency.

Key words 2,3-dihydroquinazolin-4(1*H*)-one, L-proline nitrate, ionic liquid, cyclocondensation reaction

Organic chemists from academia and industry are increasingly aware of the goals of sustainable and green chemistry.[1] With this view, green chemistry metrics such as the E-factor and atom-economy concept have played a significant role in the assessing of synthetic protocols. Monitoring these metrics proves to be helpful in minimizing waste generation during organic synthesis.[2] In this context, ionic liquids (ILs) have played a crucial role in avoiding the entry of waste chemical streams in the environment. Thus, catalysis by ILs is proving to be a means of achieving organic transformations in a green manner.[3] Amino acids and their derivatives are considered as a prevalent natural source of quaternary nitrogen and ILs derived from these amino acids, being fully green, serve as an alternative to the traditional ILs derived from imidazole or pyridine.[4]

Quinazoline derivatives display activities of biological and pharmaceutical importance such as plant-growth regulation[5] as well as antihistaminic,[6] vasodilating,[7] antianxiety,[8] tranquilizing,[9] antitumor,[10] antidepressant,[11] antidefibrillatory,[12] antihypertensive,[13] CNS stimulant,[14] and analgesic[15] properties. Quinazoline derivatives have also proven effective as insecticides, fungicides, and bactericides.[16] In addition to this, quinazolinone scaffolds have also found application in organic electroluminescence devices.[17]

Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones is usually achieved with a variety of acid catalysts[18] and certain ionic liquids.[19] In continuation of our endeavors in the development of clean and green synthetic protocols,[3] we herein disclose an efficient method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by an intramolecular one-pot cyclocondensation of anthranilamide with aldehydes employing inexpensive, recyclable L-proline nitrate (10 mol%) as an efficient catalyst (Scheme 1).



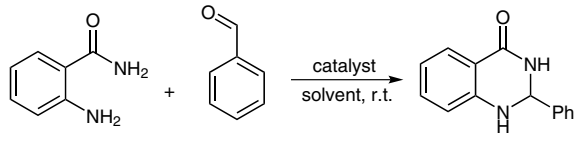
Scheme 1 Efficient access to 2,3-dihydroquinazolin-4(1*H*)-ones using L-proline nitrate

The reaction of anthranilamide (**1**) and benzaldehyde (**2a**) was opted for model studies. Gratifyingly, the desired product **3a** was achieved in 96% of yield; the presence of 10 mol% of L-proline nitrate proving vital in conjunction with acetonitrile as solvent at ambient temperature in 20 minutes (Table 1, entry 10). In the absence of catalyst, the product was only obtained in low yield (Table 1, entry 1). A catalyst loading of 10 mol% proved sufficient for nearly complete transformation (96%; Table 1, entry 10), while increasing the catalyst loading to 20 mol% neither improved the yield nor reduced the reaction time (Table 1, entry 11). Classical ILs are effective in the sense of catalytic reusability but require harsh reaction conditions (Table 1, entries 3 and 4).

We then tested various solvents such as methanol, water, dichloromethane, toluene, and acetonitrile, out of which acetonitrile proved to be most suitable for this trans-

formation giving higher yields with easier workup (Table 1, entry 10). The workup involved simple filtration of the crude reaction mass to afford sufficiently pure product that could be recrystallized from hot ethanol if necessary.

Table 1 Optimization for the Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-one



1 **2a** **3a**

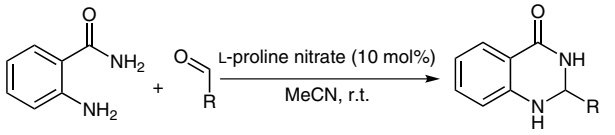
Entry	Catalyst (mol%)	Solvent	Time	Yield (%)[a]
1	–	MeCN	15 h	34
2	p-TsOH (30)	MeCN	2 h	80
3	–	[bmim]PF_6[b]	35 min	89[19a]
4	TBAB[c]	–	1.5 h	82[19b]
5	L-proline nitrate (10)	toluene	5 h	60
6	L-proline nitrate (10)	H_2O	3 h	20
7	L-proline nitrate (10)	CH_2Cl_2	2.5 h	45
8	L-proline nitrate (10)	MeOH	1 h	67
9	L-proline nitrate (5)	MeCN	1 h	72
10	L-proline nitrate (10)	MeCN	20 min	96
11	L-proline nitrate (20)	MeCN	20 min	96

[a] Isolated yields.
[b] Reaction carried out at 75 °C.
[c] Reaction carried out at 100 °C under N_2 atmosphere.

The filtrate containing IL was evaporated under reduced pressure. The residue was washed with water to give an aqueous solution of the catalyst. The bulk of the water was removed under reduced pressure, and the last traces of water were eliminated azeotropically with toluene to recover the catalyst ready for the next cycle. Even after the 6th cycle the recovered catalyst gave the desired product in >90% yield. This protocol has favorable green chemistry metrics such as a small E-factor (0.175) and process mass intensity (PMI = 4.375), higher atom economy (AE = 92.49%) and reaction mass efficiency (RME = 85.09%).

With the optimum reaction conditions established, we next explored the scope of substrates in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones (Table 2).[20] Aromatic aldehydes with electron-donating as well as electron-withdrawing substituents reacted smoothly, affording good to excellent yields of 2,3-dihydroquinazolin-4(1*H*)-ones. A variety of aromatic aldehydes with different substituent at the 2-, 3-, or 4-positions reacted readily to afford product formation with better yields.[21–24] Aliphatic aldehydes also reacted smoothly and gave good yields of products (Table 2, product **30**).

Table 2 L-Proline Nitrate Catalyzed Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-one Derivatives



2a–o **3a–o**

Product	R	Yield (%)[a]	mp (°C)	
			Observed	Lit.
3a	Ph	96	218–219	219–220[18b]
3b	4-$MeOC_6H_4$	88	192–193	189–190[18b]
3c	4-ClC_6H_4	75	206–208	205–206[18b]
3d	4-FC_6H_4	72	200–202	199–200[18b]
3e	4-BrC_6H_4	86	198–199	195–197[25]
3f	4-$Me_2NC_6H_4$	77	220–222	228–229[18b]
3g	4-*i*-PrC_6H_4	87	168–170	162–164[26]
3h	3,4,5-$(MeO)_3C_6H_2$	76	200–202	193–194[27]
3i	2-furyl	74	167–168	167.2–168.5[18b]
3j	3-MeO-4-HO C_6H_3	75	219–221	226–227[18a]
3k	2-HO	87	210–211	206–208[25]
3l	3-HO	90	208–210	209[28]
3m	4-HO	90	280–281	279–281[18b]
3n	4-O_2N	85	200–202	212.5–214.8[18b]
3o	*n*-Pr	70	165–166	162–164[29]

[a] Isolated yield.

Thus, we present L-proline nitrate as a green and efficient catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via one-pot cyclocondensation of anthranilamides and substituted aromatic/aliphatic aldehydes under mild conditions.

Acknowledgment

This research was supported by UGC New Delhi, India (F. no. 41-335/2012 (SR) dt.13.07.2012).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560483.

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(20) **General Procedure**
A mixture of anthranilamide (1.46 mmol), aldehyde (1.46 mmol), and L-proline nitrate (10 mol%) was stirred at r.t. in MeCN (0.5 mL). The progress of the reaction was monitored by TLC. After completion of reaction, the solid obtained was filtered and recrystallized from EtOH to give **3a**–**o**. To recover the catalyst, the filtrate was evaporated under reduced pressure. The residue obtained was washed with a small quantity of H_2O. This was again removed under reduced pressure, and the last traces of H_2O were removed azeotropically with a small volume of toluene to obtain the catalyst in a suitable form for the next reaction.
(21) **Representative Characterization Data**
Compound **3g**: white solid; yield 87%; mp 168–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.24 (s, 1 H, NH), 7.07 (s, 1 H, NH), 7.62 (d, *J* = 7.6 Hz, 1 H, Ar), 7.34 (d, *J* = 7.6 Hz, 1 H, Ar), 7.13 (d, *J* = 6.2 Hz, 1 H, Ar), 6.86–6.65 (m, 5 H, 1 NH, 4 Ar), 6.00 (s, 1 H), 2.88 (sept, *J* = 7.2 Hz, 1 H, $CH(CH_3)_2$), 1.17 [d, *J* = 7.2Hz, 6 H, $CH(CH_3)_2$].
(22) Compound **3k**: white solid; yield 87%; mp 210–211 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.86 (s, 1 H, OH), 7.94 (s, 1 H, NH), 6.95 (s, 1 H, NH), 7.62 (d, *J* = 7.6 Hz, 1 H, Ar), 7.34 (d, *J* = 7.6 Hz, 1 H, Ar), 7.13 (d, *J* = 6.2 Hz, 1 H, Ar), 6.86–6.65 (m, 5 H, 1 NH, 4 Ar), 6.00 (s, 1 H).
(23) Compound **3l**: white solid; yield 90%; mp 208–210 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12 (s, 1 H, OH), 7.69 (s, 1 H, NH), 6.29 (s, 1 H, NH), 7.68 (d, *J* = 7.64 Hz, 1 H, Ar), 7.23–6.64 (m, 8 H, Ar), 5.66 (s, 1 H).
(24) Compound **3m**: white solid; yield 90%; mp 280–281 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.55 (s, 1 H, OH), 8.12 (s, 1 H, NH), 6.95 (s, 1 H, NH), 7.60 (d, *J* = 6.8 Hz, 1 H, Ar), 7.31–7.21 (m, 3 H, Ar), 6.77–6.64 (m, 4 H, Ar), 5.64 (s, 1 H).
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