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Efficient synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones using $KAl(SO_4)_2{\cdot}12H_2O$ as a reusable catalyst in water and ethanol

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Abstract—$KAl(SO_4)_2{\cdot}12H_2O$ was found to catalyze efficiently a one-pot three-component cyclocondensation of isatoic anhydride and primary amines or ammonia sources such as $(NH_4)_2CO_3$, NH_4OAc and NH_4Cl with aromatic aldehydes under mild conditions to afford the corresponding mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in good yields.

1. Introduction

A literature survey of important and valuable physiological properties for mono- and disubstituted 2,3-dihydroquinazoline-4(1*H*)-ones includes analgesic, antitumour, anticancer, diuretic and herbicide activities.[1] In addition, these compounds can easily be oxidized to their quinazolin-4(3*H*)-one analogues,[2] which also include important pharmacologically active compounds.[3]

Several methods have been reported for the synthesis of 2,3-dihydroquinazolinones.[3–7] However, these methods suffer from lengthy procedures and/or low yields and vigorous conditions.[3–7]

One-pot transformations, particularly multi-component reactions (MCRs) are of current interest to organic chemists.[8] Since the first MCR reported in 1850 by Strecker,[9] this methodology has emerged as an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and diversity can be achieved simply by varying the reaction components.[8,9] MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening.[10] Very recently, we reported the preparation of 2,3-disubstituted quinazolin-4(3*H*)-ones via multi-component reactions.[11] Now, we have designed a three-component one-step synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. For this, the use of $KAl(SO_4)_2{\cdot}12H_2O$ (alum), which is relatively non-toxic and inexpensive, was at the centre of our study. In the course of our work on applications of $KAl(SO_4)_2{\cdot}12H_2O$ in organic reactions, we have found that it is an effective promoter for the preparation

Table 1. Screening of Lewis acids[a]

LA[b]	Time (h)	Yield[c] (%)	
		H_2O	EtOH
KBr	30	0	0
KCl	30	0	0
LiCl	30	0	0
LiBr	30	0	0
I_2	30	0	0
$AlCl_3$	7	25	40
$NH_4Al(SO_4)_2{\cdot}12H_2O$	30	21	35
$KAl(SO_4)_2{\cdot}12H_2O$	4	79	88

[a] Yields of **4a** using different LAs in the reaction of isatoic anhydride, ethylamine and benzaldehyde.
[b] For all reactions 0.5 mmol Lewis acid was used.
[c] Isolated yields based on isatoic anhydride.

Keywords: $KAl(SO_4)_2{\cdot}12H_2O$; Multi-component reaction; Cyclocondensation; 2,3-Dihydroquinazolin-4(1*H*)-ones; Reusable catalyst.
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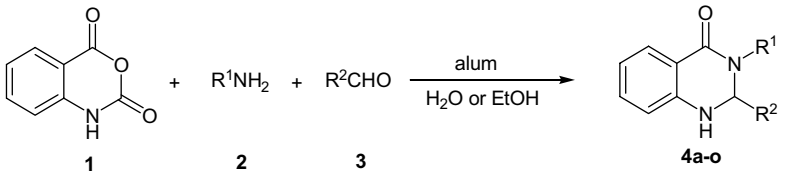


Scheme 1.

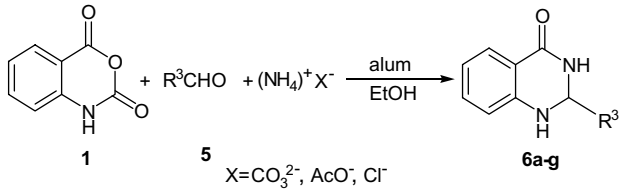
of mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones.

When a mixture of isatoic anhydride **1**, ethylamine **2** and benzaldehyde **3** in H_2O or EtOH was stirred under reflux in the presence of a catalytic amount of alum, the reaction was completed within 1 h and 4 h, respectively. Work-up gave **4a** in 79% and 88% yields, respectively (Table 1 and Scheme 1).

After screening several Lewis acids (LAs), we found that alum was the best promoter for the reaction of isatoic anhydride **1**, ethylamine **2** and benzaldehyde **3** (Table 1).

Encouraged by this success, we examined the reaction of isatoic anhydride with a range of other aromatic aldehydes carrying either electron-releasing or electron-withdrawing substitutes, affording high yields of products. Aliphatic amines gave the products in shorter periods compared to aromatic analogues. The optimized results are summarized in Table 2.

We also checked the reusability of the catalyst by recovering the alum and using it for new runs and found that the catalyst could be reused several times without any decrease in the product yield. An example is shown for the reaction of ethylamine with isatoic anhydride and benzaldehyde (Table 2, **4a**). The catalyst can be removed from the aqueous phase by removing the water under vacuum then washing with EtOH and drying at rt.



Scheme 2.

When isatoic anhydride **1**, aromatic aldehydes **5** and ammonium salts such as ammonium carbonate, ammonium chloride and ammonium acetate were used as the source of ammonia,[12] in the presence of alum with stirring for 4–5 h in EtOH under reflux, 2-aryl substituted 2,3-dihydroquinazoline-4(1*H*)-ones **6a**–**g** were prepared in good yields (Scheme 2). The optimized results are summarized in Table 3.

Presumably, the reaction proceeds through condensation of isatoic anhydride **1** with primary amine **2** followed by decarboxylation to yield the corresponding 2-aminobenzamide **7**.[13] Condensation of the aromatic aldehyde with the amino group of **7** then gives imine **8** which undergoes cyclization to afford the dihydroquinazoline product **4** (Scheme 3). Support for this mechanism was obtained when *N*-methyl isatoic anhydride **9** was reacted with ethylamine and benzaldehyde under the same conditions; only 2-*N*-methylamino ethylbenzamide[15] (**7a**) was obtained (Scheme 4).

Table 2. Alum-catalyzed synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones by the reaction of isatoic anhydride with primary amines and aromatic aldehydes

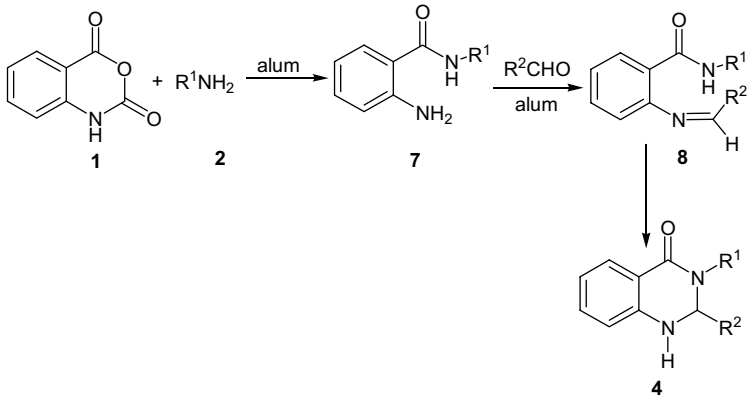
4	R^1	R^2	Time (h)		Yield[a] (%)		Mp (°C)
			H_2O	EtOH	H_2O	EtOH	
a	Et	Ph	1	4	79, 75, 76[b]	88, 85, 87[b]	134–137[2a]
b	Et	*p*-ClC_6H_4	1	4	81	87	132–135[2a]
c	Et	*p*-$O_2NC_6H_4$	1	3	79	91	160–161[2a]
d	Et	*m*-$O_2NC_6H_4$	1	4	80	92	176–178[2a]
e	Et	*p*-$CH_3OC_6H_4$	1	5	70	80	124–126[2a]
f	Ph	Ph	1	4	65	78	205–206[7b]
g	Ph	*m*-$O_2NC_6H_4$	1	5	79	85	186–188[7b]
h	Ph	*p*-$O_2NC_6H_4$	1	4.5	67	76	195–197[7b]
i	Ph	*p*-ClC_6H_4	1	5	73	81	214–217[7b]
j	Me	Ph	1	4	69	78	164–165[2a]
k	Me	*p*-$CH_3OC_6H_4$	1	4.5	64	76	145–146[2a]
l	Me	*p*-ClC_6H_4	1	5	65	78	188–190[2a]
m	*p*-ClC_6H_4	Ph	1	4	73	80	214–216[7b]
n	*n*-Pr	*p*-$O_2NC_6H_4$	1	4	65	76	120–121[15]
o	Et	*p*-HOC_6H_4	1	4	70	83	180–182[15]

[a] Isolated yield based on isatoic anhydride.
[b] The catalyst was reused for three runs.

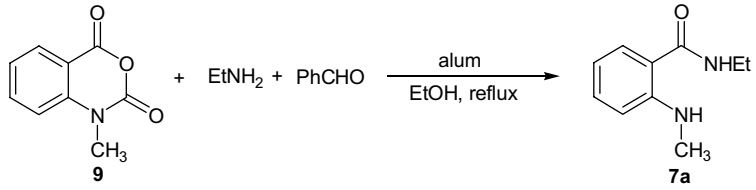
Table 3. Alum-catalyzed synthesis of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones by the reaction of isatoic anhydride with ammonium salts and aromatic aldehydes in EtOH

6	R^3	X	Time (h)	Yield [a] (%)	Mp (°C)
a	Ph	CO_3^{2-}	4	83	218–220[5]
b	*p*-ClC_6H_4	CO_3^{2-}	4	79	198–200[5]
c	*p*-$CH_3OC_6H_4$	CO_3^{2-}	6	81	178–180[5]
d	*o*-$CH_3OC_6H_4$	CO_3^{2-}	4	75	165–167[1e]
e	*p*-$CH_3C_6H_4$	CO_3^{2-}	4	76	233–234[14]
f	*m*,*p*-$(CH_3O)_2C_6H_3$	CO_3^{2-}	4	72	210–213[1e]
g	2-Furyl	CO_3^{2-}	4	78	165–167[14]
a	Ph	AcO^-	4	71	218–220[5]
b	*p*-ClC_6H_4	AcO^-	5	80	198–200[5]
c	*p*-$CH_3OC_6H_4$	AcO^-	6	71	178–180[5]
d	*o*-$CH_3OC_6H_4$	AcO^-	4	72	165–167[1e]
e	*p*-$CH_3C_6H_4$	AcO^-	5	69	233–234[14]
f	*m*,*p*-$(CH_3O)_2C_6H_3$	AcO^-	5	72	210–213[1e]
g	2-Furyl	AcO^-	4	75	165–167[14]
a	Ph	Cl^-	4	70	218–220[5]
b	*p*-ClC_6H_4	Cl^-	5	77	198–200[5]
c	*p*-$CH_3OC_6H_4$	Cl^-	6	71	178–180[5]
d	*o*-$CH_3OC_6H_4$	Cl^-	4	70	165–167[1e]
e	*p*-$CH_3C_6H_4$	Cl^-	5	72	233–234[14]
f	*m*,*p*-$(CH_3O)_2C_6H_3$	Cl^-	5	74	210–213[1e]
g	2-Furyl	Cl^-	4	73	165–167[14]

[a] Isolated yield based on isatoic anhydride.



Scheme 3.



Scheme 4.

In conclusion, we have described a successful strategy for the efficient and convenient synthesis of mono- and disubstituted 2,3-dihydroquinazolinones in a one-pot, three-component cyclocondensation reaction of isatoic anhydride, aromatic aldehydes and primary amines or ammonium salts using the inexpensive, non-toxic and easily available $KAl(SO_4)_2{\cdot}12H_2O$ as catalyst in H_2O or EtOH. The method offers several advantages including high yields of products, a recyclable catalyst and an easy experimental work-up procedure.

2. General procedure

Preparation of mono- and disubstituted 2,3-dihydroquinazoline-4(1*H*)-ones in EtOH. To a solution of isatoic anhydride (1 mmol), primary amine (1.1 mmol) or an ammonium salt (ammonium carbonate 0.6 mmol, ammonium acetate 1.2 mmol or ammonium chloride 1.2 mmol) and aldehyde (1 mmol) in ethanol (5 mL) was added alum (0.15 g, 0.4 mmol). The mixture was heated at reflux for the specified period of time (see

Tables 2 and 3). After completion of the reaction as indicated by TLC (eluent: 1/3 ethyl acetate–*n*-hexane), the solid catalyst was separated by filtration. Water (10 mL) was added and the precipitated product was filtered and recrystallized from EtOH.[15]

Preparation of 2,3-disubstituted 2,3-dihydroquinazoline-4(1*H*)-ones in H_2O. Alum (0.2 g) was added to a mixture of isatoic anhydride (1 mmol), primary amine (1.1 mmol) and aldehyde (1 mmol) in water. The mixture was heated at reflux for 1 h (see Table 2). After completion of the reaction, the solid residue was separated, washed with water (10 mL) and recrystallized from ethanol.

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References and notes

1. (a) Hour, M.; Huang, L.; Kuo, S.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. *J. Med. Chem.* **2000**, *43*, 4479–4487; (b) Misra, V. S.; Saxena, V. K.; Srivastava, R. *Indian J. Pharm. Sci.* **1983**, *45*, 207–211; (c) Kacker, I. K.; Zaheer, S. H. *J. Indian Chem. Soc.* **1951**, *28*, 344–348; (d) Gupta, R. C.; Nath, R.; Shanker, K.; Bhargava, K. P.; Kishore, K. *J. Indian Chem. Soc.* **1979**, *56*, 219–220; (e) Parmar, S. S.; Kumar, R.; Arora, R. C. *Indian J. Med. Res.* **1969**, *57*, 245–248.
2. (a) Abdel-Jalil, R. J.; Volter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475–3476; (b) Lopez, S. E.; Rosales, M. E.; Urdaneta, N.; Godoy, M. V.; Charris, J. E. *J. Chem. Res. (S)* **2000**, 258–259; (c) Rao, V. B.; Hanumanthu, P.; Rantnam, C. V. *Indian J. Chem.* **1979**, *18B*, 493–496.
3. (a) Johne, S. *Pharmazie* **1981**, *36*, 583–596; (b) Mannschreck, A.; Koller, H.; Stuhler, G.; Davies, M. A.; Traber, J. E. *J. Med. Chem.* **1994**, *19*, 381–383; (c) Sharma, S. D.; Kaur, V. *Synthesis* **1989**, 677–680; (d) Cizmarik, J.; Trupe, J. *Pharmazie* **1987**, *42*, 139–140; (e) Kung, P. P.; Casper, M. D.; Cook, K. L.; Willson-Lin-gardo, L. *J. Med. Chem.* **1999**, *42*, 4705–4713; (f) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bachheler, L. T.; Diamond, S.; Jeffey, S.; Trainor, G. L.; Anderson, P. S.; Erickson-Vitanen, K. *J. Med. Chem.* **2000**, *43*, 2019–2030; (g) Liu, J. F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. *Tetrahedron Lett.* **2005**, *46*, 1241–1244.
4. Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webster, W. *J. Org. Chem.* **1969**, 887–892.
5. Su, W.; Yang, B. *Aust. J. Chem.* **2002**, *55*, 695–697.
6. Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Hu, H. *Tetrahedron Lett.* **2003**, *44*, 3199–3201.
7. (a) Sadanandam, Y. S.; Reddy, K. R. M.; Rao, A. B. *Eur. J. Org. Chem.* **1987**, *22*, 169–173; (b) Reo, V. B.; Ratnam, C. V. *Indian J. Chem.* **1979**, *18B*, 409–412.
8. For reviews, see: (a) Pandey, G.; Singh, R. P.; Gary, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 2137–2140; (b) Werner, B.; Domling, A. *Molecules* **2003**, *8*, 53–66; (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210; (d) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888; (e) Terret, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135–8173.
9. Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27–45.
10. (a) Domling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313; (b) Weber, L. *Drug Discovery Today* **2002**, *7*, 143–147.
11. Dabiri, M.; Salehi, P.; Mohammadi, Ali A.; Baghbanzadeh, M. *Synth. Commun.* **2005**, *35*, 287–295.
12. (a) Tewari, N.; Dwivedi, N.; Tripathi, R. P. *Tetrahedron Lett.* **2004**, *45*, 9011–9014; (b) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827–828.
13. Dabiri, M.; Salehi, P.; Mohammadi, Ali A.; Baghbanzadeh, M.; Khozehgiry, Gh. *J. Chem. Res. (S)* **2004**, 570–572.
14. Yale, L. H.; Kalkstein, M. *J. Med. Chem.* **1967**, *10*, 334–336.
15. $C_{17}H_{17}N_3O_3$ **4n**: IR (KBr) (ν_{max}, cm^{-1}): 3420, 1680 (C=O); ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 0.94 (3H, t, $J = 7.3$ Hz), 1.64 (2H, m), 2.77 (1H, ddd, $J = 14.1$, 8.59, 5.8 Hz), 4.05 (1H, ddd, $J = 13.9$, 8.7, 6.6 Hz), 5.82 (1H, s, CH), 6.5–8.2 (8H, m, arom); ^{13}C NMR ($CDCl_3$) δ_C: 12.5, 22.3, 48.1, 71.9, 116.0, 117.4, 120.9, 125.3 (2C), 128.3 (2C), 129.5, 134.9, 145.4, 148.3, 149.2, 164.1 (C=O); MS (*m*/*z*, %): 311 (M^+, 64), 174 (47.6), 119 (45.2), 105 (44.3), 77 (51.6).
$C_{16}H_{16}O_2N_2$ **4o**: IR (KBr) (ν_{max}, cm^{-1}): 3440, 1680 (C=O); ^1H NMR (DMSO-d_6 500 MHz) δ_H: 1.0 (3H, t, CH_3, $J = 7.08$ Hz), 2.83 (1H, dq, $J = 13.6$, 7.02 Hz), 3.71 (dq, 1H, $J = 13.6$, 7.16 Hz), 5.73 (1H, d, $J = 1.9$ Hz), 6.6–6.7 (4H, m), 7.11–7.18 (3H, m), 7.20 (1H, d, $J = 1.9$, NH), 7.62 (1H, dd, $J = 7.6$, 1.4 Hz), 9.48 (1H, s, OH); ^{13}C NMR (DMSO-d_6) δ_C: 14.6, 71.6, 115.6, 116.3, 116.7 (2C), 118.5, 128.9, 129.3 (2C), 133.0, 134.4, 148.1, 159.2, 163.3 (C=O); MS (*m*/*z*, %): 268 (M^+, 60), 174 (67.1), 105 (53.5), 77 (40.5).
$C_{10}H_{14}N_2O$ **7a**: mp 88–90 °C; IR (KBr) (ν_{max}, cm^{-1}): 3440, 3290, 1620 (C=O); ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 1.24 (3H, t, $J = 1.25$ Hz), 2.98 (3H, s), 3.45 (2H, q, $J = 7.25$ Hz), 6.03 (1H, br d, NH), 6.5–7.3 (4H, m), 7.49 (1H, br d, NH); ^{13}C NMR ($CDCl_3$) δ_C: 14.9, 29.7, 34.5, 111.1, 114.5, 115.4, 127.0, 132.6, 150.3, 169.8; MS (*m*/*z*, %): 178 (M^+, 70), 119 (60.4), 104 (69.5), 77 (52.2).