Efficient and practical one-pot route to synthesise quinazolin4(3*H*)-ones using trifluoromethanesulfonic anhydride and 2-chloropyridine

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An effective, novel and rapid one-pot three-component route to quinazolin-4(3H)-ones from commercially available starting materials is described. Isatoic anhydride reacts with acyl chlorides and different amines using a combination of trifluoromethanesulfonic anhydride (Tf_2O) and 2-chloropyridine (2-ClPy) to produce the corresponding quinazolinone derivatives in good to excellent yields.

Keywords: amines, isatoic anhydride, 4(3*H*)-quinazolinones, multicomponent reactions, trifluoromethanesulfonic anhydride, 2-chloropyridine

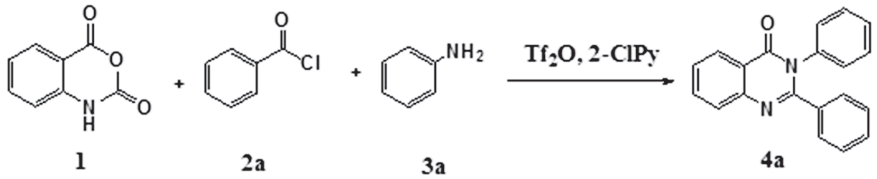
Quinazolinone derivatives are essential units in a wide range of relevant pharmacophores with a broad spectrum of abilities.[1] Due to their wide range of pharmacological and therapeutic activities including anticonvulsant,[2] anti-inflammatory,[3] hypolipidemic,[4] anticancer[5] and anti-ulcer,[6] the synthesis of quinazolinone moieties as a privileged class of fused heterocyclic compounds[7] has attracted researchers' attention. In recent years, several synthetic routes have been introduced for the preparation of 4(3*H*)-quinazolinone derivatives in which the condensation of a 2-aminobenzoic acid or its derivatives with amides has been mentioned as the most common synthetic approach. Various procedures which have been recently reported involve the cyclocondensation reaction using different substrates such as benzyl halides, amines and isatoic anhydride,[8] multi-step reactions under microwave irradiation[9] or in ionic liquids,[10] and also there are some reports on metal-catalysed examples.[11] Meanwhile, a method has been reported for the one-pot synthesis of 4(3*H*)-quinazolinone derivatives using isatoic anhydride–anthranilic acid, orthoesters and amines.[12] To our knowledge, there have been few reports on the one-pot synthesis of quinazolin-4(3*H*)-ones using acyl halides as starting materials.[13] There are a few methods using an orthoester in place of the acid chloride that have been reported,[14–16] but these pathways have some drawbacks such as low yields, long reaction times, high temperatures and harsh reaction conditions, difficult and time consuming work-up, and use of expensive reagents and catalysts. Therefore, the development of a novel and efficient methodology for the synthesis of quinazolin-4(3*H*)-ones is timely. Focusing on the pharmacological importance of 4(3*H*)-quinazolinones and as a continuation of our research on the development of new routes for the synthesis of different heterocyclic scaffolds, we wish to introduce a convenient protocol to prepare 2,3-disubstituted quinazolinones by a one-pot three-component condensation reaction between isatoic anhydride, acyl chlorides, and amines in the presence of trifluoromethanesulfonic anhydride (Tf_2O) and 2-chloropyridine (2-ClPy).

Results and discussion

Amides are attractive starting materials because they are easily available, but amides themselves are rarely used as precursors in organic synthesis due to their stability. Due to this low reactivity of amides, there are several reports on the activation of the amide moiety. The combination of trifluoromethanesulfonic anhydride (Tf_2O) and pyridine or 2-chloropyridine (2-ClPy) is the most attractive and feasible example.[16–18]

We believed that the combination of trifluoromethanesulfonic anhydride (Tf_2O) and 2-chloropyridine (2-ClPy) would be useful for our purpose. The three component one-pot condensation of isatoic anhydride **1**, benzoyl chloride **2a**, and aniline **3a** was selected as a model reaction. The reaction condition including the solvent, the amount of Tf_2O and 2-ClPy, reaction time and required temperature are optimised. As shown in Table 1, among three different conditions, CH_2Cl_2,

Table 1 Optimisation of reaction conditions[a]



1 **2a** **3a** **4a**

Entry	Solvent	Temperature/°C	Time/h	(Tf_2O/2-ClPy)/equiv.	Yield/%
1	DMF	110	24	–	20
2	DMF	110	2	0.5/0.5	90
3	DMF	r.t.	2	0.5/0.5	45
4	DMF	r.t.	2	1 /1	57
5	–	110	2	0.5/0.5	90[b]
6	DCM	r.t.	2	0.5/0.5	35
7	**DCM**	**40**	**2**	**0.5/0.5**	89
8	DCM	40	2	1 /1	92
9	DCM	40	4	0.25/0.25	46

[a]Isatoic anhydride (**1**) (1.0 mmol), amine (**3a**) (1.1 mmol), acyl chloride, (**2a**) (1.1 mmol).
[b]Reaction under solvent-free conditions.

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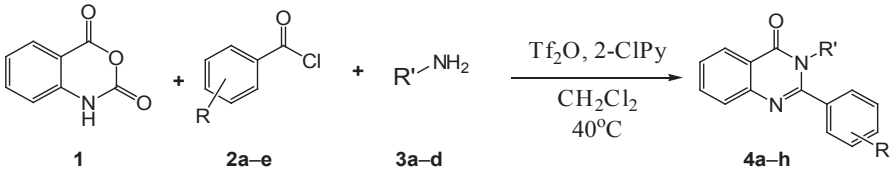

Scheme 1 One-pot synthesis of 2,3-disubstituted quinazolin-4-(3*H*)-one derivatives.

40 °C and 0.5 equiv. of Tf_2O and 2-ClPy led to the best results. No quinazolinone **4a** was formed in the absence of Tf_2O and 2-ClPy, and also using the higher amounts of Tf_2O and 2-ClPy showed no significant improvement in this reaction.

Then, a wide range of structurally diverse acyl chlorides **2**, amines **3**, and isatoic anhydrides **1** were reacted under the optimum conditions (Scheme 1) and the results are summarised in Table 2. In all cases, the three component reaction proceeded smoothly to afford the corresponding quinazolin-4(3*H*)-one derivatives in good to excellent yields. The results also showed that aromatic amines reacted to give the corresponding quinazolinones in good yields. Also it was found that amines or acyl halides having an electron-donating or electron withdrawing group tolerated the cyclisation reaction to give the corresponding quinazolinone in satisfactory yields. It is concluded that this procedure is an efficient method for the preparation of quinazolin-4(3*H*)-one derivatives from isatoic anhydride, acyl halides and amines under mild conditions.

Conclusions

In conclusion, we have developed a convenient one-pot approach for the synthesis of quinazolin-4(3*H*)-one derivatives from isatoic anhydride, different amines and acyl chlorides by the electrophilic activation of amides using the catalytic combination of trifluoromethanesulfonic anhydride (TF_2O) and 2-chloropyridine (2-ClPy). The present method is highly efficient and also the substrates are readily available. The efficiency, mild conditions, short reaction time, easy isolation of the products, simplicity and high yields are some of the remarkable synthetic advantages of this protocol.

Experimental

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-500 instrument, using TMS as an internal standard. Elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode. All reagents and solvents were purchased from Aldrich or Merck and used without any purification.

Synthesis of quinazolin-4(3H)-ones; general procedure

A solution of Tf_2O (1 mmol, 50 mol%) in DCM (1 mL) was added dropwise by a syringe to a mixture of isatoic anhydride (**1**) (2.0 mmol), amine (**3a**–**d**) (2.2 mmol), acyl chloride (**2a**–**e**) (2.2 mmol), and 2-ClPy (1 mmol, 50 mol%) in DCM (2 mL) under an inert atmosphere at –78 °C. After 15 min, the reaction mixture was then warmed to 40 °C and stirred until completion for 2 h. In all cases, the progress of the reaction was monitored by TLC. After 2 h, the reaction mixture was diluted with water. The organic layer was washed with the saturated aqueous Cu_2SO_4 solution (5 mL), brine (5 mL × 2), and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was recrystallised from EtOH to give 2,3-disubstituted quinazolin-4-(3*H*)-one derivatives in high yield. The observed and literature melting points are shown in Table 2.

*2,3-Diphenylquinazolin-4(3*H*)-one* (**4a**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.13–7.16 (m, 2H) 7.20–7.24 (m, 2H), 7.27–7.34 (m, 6H), 7.50–7.53 (m, 1H), 7.81–7.85 (m, 2H), 8.22 (d, J=8.0 Hz,1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 122.1, 128.3, 128.4, 128.9, 129.1, 129.5, 130.1, 130.3, 130.5, 135.8, 136.2, 138.9, 148.6, 154.3, 163.5.

*2-Phenyl-3-(*p*-tolyl)quinazoline-4(3*H*)-one* (**4b**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.18 (s, 3H), 7.02–7.05 (m, 2H), 7.11–7.15 (m, 2H), 7.21–7.25 (m, 3H), 7.33–7.38 (m, 2H), 7.50–7.53 (m, 1H), 7.73 (s, 2H), 8.31(d, J=7.5 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 20.1, 120.3, 126.1, 127.5, 127.7, 128.4, 128.6, 129.0, 129.2, 129.5, 134.5, 135.4, 135.9, 138.1, 146.2, 154.2, 161.8.

*2-(*p*-Tolyl)-3-phenylquinazoline-4(3*H*)-one* (**4c**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.25 (s, 3H), 7.11 (d, J=7.5 Hz, 2H), 7.18 (d, J=8 Hz, 2H), 7.25 (d, J=8 Hz, 2H), 7.32–7.38 (m, 3H), 7.55 (s, 1H), 7.88 (s, 2H), 8.39 (d, J=7.5 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 20.5, 122.2, 126.4, 126.8, 127.5, 128.4, 128.8, 129.0, 129.3, 133.8, 134.6, 136.7, 140.5, 146.8, 156.5, 162.1.

*2-(4-Chlorophenyl)-phenylquinazoline-4(3*H*)-one* (**4d**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.15–7.22 (m, 4H), 7.29–7.36 (m, 4H), 7.53–7.58 (m, 2H), 7.80 (s, 1H), 8.35 (d, J=7.5 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 122.0, 127.4, 127.6, 127.9, 128.5, 128.8, 129.3, 129.7, 130.8, 134.1, 134.5, 135.7, 137.8, 147.8, 154.5, 162.5.

*3-(4-Chlorophenyl)-2-phenylquinazoline-4(3*H*)-one* (**4e**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.08–7.11 (m, 2H), 7.27–7.34 (m, 7H), 7.55 (t, J=7.6 Hz, 1H), 7.74 (t, J=7.3 Hz, 1H), 7.92–7.96 (m, 1H), 8.36 (d, J=7.5 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 121.4, 126.2, 126.3, 127.2, 128.5, 129.2, 129.3, 129.8, 130.6, 133.5, 134.4, 135.2, 137.3, 145.4, 155.5, 161.3. (The characterisation of this novel product is not formally complete but is well supported by the data given and the formation of the other products.)

Table 2 Synthesis of quinazolin-4-(3*H*)-one derivatives[a]

Product	R	R'	Yield /%	M.p./°C	
				Observed	Reported[Ref]
4a	H	C_6H_5	89	159–160	158[20]
4b	H	4-MeC_6H_4	76	178–179	180–181[21]
4c	4-Me	C_6H_5	78	173–175	171–172[8]
4d	4-Cl	C_6H_5	82	172–174	177–178[8]
4e	2-Cl	C_6H_5	85	196–199	–
4f	H	4-ClC_6H_4	86	196–199	190–191[8]
4g	H	4-$MeOC_6H_4$	83	198–200	199–200[8]
4h	4-MeO	C_6H_5	88	155–157	154–155[22]

[a]Isatoic anhydride (2.0 mmol), amine (2.2 mmol), acyl chloride (2.2 mmol), 2-ClPy (1 mmol, 50 mol%) Tf_2O (1 mmol, 50 mol%) in DCM, 40 °C, 2 h.

*3-(4-Methoxyphenyl)-2-phenylquinazolin-4(3*H*)-one* (**4f**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.85 (s, 3H), 6.80–6.85 (m, 2H), 7.01–7.05 (m, 2H), 7.27 (s, 3H), 7.33–7.37 (m, 2H), 7.52 (t, J=7.2 Hz, 1H), 7.80–7.84 (m, 2H), 8.21 (d, J=7.5 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 3.42, 118.3, 122.7, 126.4, 126.9, 127.2, 128.2, 128.7, 129.4, 130.2, 130.7, 133.2, 134.2, 145.2, 153.2, 160.1,, 163.4.

*2-(4-Methoxyphenyl)-3-phenylquinazolin-4(3*H*)-one* (**4g**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.84 (s, 3H), 6.84 (d, J=8.0 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H), 7.30–7.36 (m, 5H), 7.51 (s, 1H), 7.71–7.77 (m, 2H), 8.30 (d, J=8.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 54.5, 113.4, 121.8, 126.0, 126.3, 126.6, 127.4, 128.2, 129.1, 129.3, 131.4, 135.6, 139.1, 146.5, 155.7, 161.2, 162.8.

*2-Phenyl-3-*o*-tolylquinazolin--4(3*H*)-one* (**4h**): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.15 (s, 3H), 7.04–7.08 (m, 1H), 7.15–7.21 (m, 6H), 7.30–7.35 (m, 2H) 7.60 (t, J=7.2 Hz, 1H), 7.73–7.78 (m, 2H), 8.20 (d, J=8.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 18.2, 122.4, 125.3, 126.3, 127.5, 127.7, 127.8, 128.3, 128.4, 129.3, 129.8, 130.2, 133.8, 134.2, 135.2, 143.1, 154.6, 155.0, 162.3.

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