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A new concise synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives†

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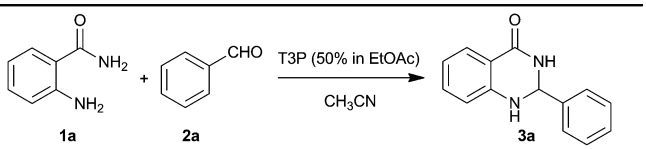
A new T3P®-assisted, convenient and efficient procedure for the synthesis of dihydroquinazolinones is described. The main advantages of this protocol include its practical simplicity, short reaction times and particularly the ease with which products are isolated.

The quinazolinone ring is observed in several important natural and synthetic organic derivatives. It has also been established as a useful privileged scaffold for library design and drug discovery applications.[1] Many 2,3-dihydroquinazolinones are reported to be interesting as anticancer, antibiotic, analgesic, antihistaminic and antidepressant agents.[2] Consequently, a number of synthetic methods have been reported for their synthesis. In particular, synthetic routes based on cyclisation of simple aminobenzamide derivatives with aldehydes employing amberlyst-15,[3] β-cyclodextrin,[4] ionic liquids,[5] ammonium chloride,[6] Brönsted and phosphoric acids,[7,8] tetrabutyl ammonium bromide,[9] $TiCl_4/Zn$[10] and cerium(IV) ammonium nitrate (CAN)[11] have been used for this purpose. However, these methods suffer from lengthy procedures and/or low yields.

We have already described the highly effective use of propylphosphonic anhydride (T3P®) in the Fischer indole synthesis, the Pictet–Spengler reaction and in the synthesis of diverse pyrazolones.[12] In continuation of our investigations, we report here the efficient and rapid synthesis of 2,3-dihydroquinazolinones catalyzed by T3P®.

Acetonitrile has been found to be one of the most effective solvent mediums for the generation of dihydroquinazolinones.[13] In a model reaction between 2-aminobenzamide (**1a**, 0.5 mmol) and benzaldehyde (**2a**, 0.5 mmol) in acetonitrile, we investigated the synthesis of dihydroquinazolinone **3a**.

Table 1 Optimization of the reaction conditions



1a 2a 3a

Entry	T3P® (equiv.)	Time (min)	Conversion[a] (%)
1	1	30	100
2	0	30	2
3	1	20	99
4	**1**	**10**	**98**
5	1	5	92
6	0.5	10	95
7	0.25	10	92

[a] Determination by LC/MS at 254 nm.

In the presence of one equivalent of T3P® (50% solution in EtOAc), a clean and complete reaction occurred at room temperature within 30 minutes (Table 1, entry 1).

To clarify the role of T3P® in this process, the same reaction was conducted without T3P® (Table 1, entry 2). Only a small amount of the expected compound (*e.g.* 2%) was observed after 30 minutes of reaction. We then explored the influence of the reaction time and the stoichiometry of T3P® on the reaction rate. A good conversion of 98% was obtained within 10 minutes using one equivalent of T3P® while 92% of conversion was obtained even with a shorter reaction time of 5 minutes (Table 1, entries 4 and 5). Decreasing the number of equivalents of T3P® to 0.5 and 0.25 equivalents, respectively, and using a reaction time of 10 minutes led to reduced conversion (entries 6 and 7, 95% and 92%, respectively), confirming the catalytic role of T3P®.

Encouraged by this success, we studied this reaction with a range of other aldehydes **2** using optimized conditions (T3P® 1 equiv., 10 minutes at room temperature in acetonitrile), furnishing the respective dihydroquinazolin-4(1*H*)-ones **4** in good yields. The results are summarized in Table 2.

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† Electronic supplementary information (ESI) available: Experimental details and ^1H and ^{13}C NMR spectra of all the compounds. See DOI: 10.1039/c3nj00618b

Table 2 Aldehyde scope of the reaction

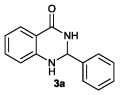
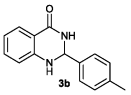
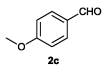
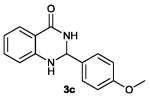
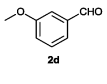
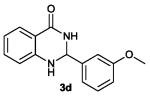
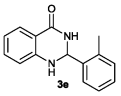
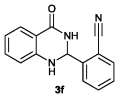
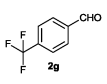
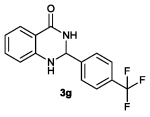
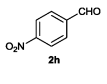
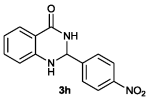
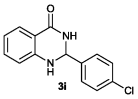
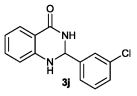
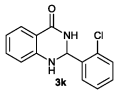
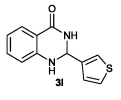
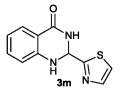
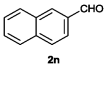
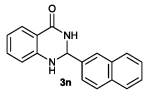
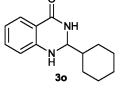
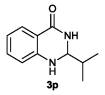
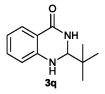
Entry	Aldehyde	Product	Time (min)	Yield[a] (%)
1			10	92
2			10	90
3			10	89
4			10	85
5			10	91
6			10	93
7			10	88
8			10	92
9			10	87
10			10	89
11			10	90
12			10	93
13			10	94
14			10	87
15			15	89

Table 2 (*continued*)

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)
16			15	85
17			15	86

[a] Reactions conducted on a 0.5 mmol scale, isolated yield.

To our delight, this process was applicable to diverse substrates. Aromatic aldehydes with electron-donating or -withdrawing substituents reacted very well, affording good to excellent yields of 2,3-dihydroquinazolinones (Table 2, entries 1 to 11). No significant differences in the yields were observed, indicating that the nature or the position of the substituent had negligible influence on the rate of the reaction. Similarly, heterocyclic aldehydes gave the expected products in excellent yields (entries 12–13).

Finally, we were also pleased to see that, even though a slightly longer reaction time was needed (15 minutes), linear or cyclic aliphatic aldehydes produced the desired compounds in good yields (Table 2, entries 15–17). The dihydroquinazolinones were generally precipitated from the reaction mixtures and simple filtration and washing with a little acetonitrile afforded the expected products in sufficient purity.

In conclusion, a simple and efficient protocol has been developed for the synthesis of 2,3-dihydroquinazolinones which are a key feature in numerous natural and synthetic therapeutic compounds. Most of the reported methods to prepare these heterocycles suffer from a longer reaction time,[4–8] a tedious procedure[11] and/or drastic conditions.[9,10] This method, employing T3P® as the catalyst, has several advantages such as a simple operational procedure, a short reaction time (10–15 minutes), the use of very mild conditions (room temperature) and an easy access to the compounds in good to excellent yields.

The synthesis of other important heterocycles by using T3P® is under investigation in our laboratory.

Experimental section

Compounds **3a**,[14] **3b**,[14] **3c**,[14] **3d**,[15] **3g**,[16] **3h**,[17] **3i**,[14] **3j**,[3] **3k**,[16] **3n**,[14] **3o**,[18] **3p**[14] and **3q**[14] are all known compounds; spectral data obtained were in agreement with the proposed structures and matched those reported in the literature.

Melting points were obtained using a Stuart Scientific SMP3 apparatus and are uncorrected.

2-(2-Methylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e)

T3P® (50% in EtOAc) (1 equiv., 0.5 mmol) was added to a solution of 2-aminobenzamide (**1a**, 0.5 mmol) and 2-methylbenzaldehyde (**2e**, 0.5 mmol) in acetonitrile (1 mL) in a sealed tube. After completion of the reaction (10 min, indicated by TLC, eluent CH_2Cl_2–MeOH 95/5), the reaction mixture was

purified by column chromatography on a silica gel on a Biotage SP4 apparatus, gradient CH_2Cl_2–MeOH 1 to 10%.

Yield: 108 mg (91% yield, white powder), m.p. (EtOH) 188–189 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.05 (br s, 1H), 7.66 (d, 1H, J = 7.6 Hz), 7.57 (dd, 1H, J = 7.6 Hz), 7.30–7.21 (m, 4H), 6.86 (br s, 1H), 6.76 (d, 1H, J = 7.6 Hz), 6.72–6.68 (m, 1H), 6.00 (s, 1H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 164.0, 148.5, 138.0, 136.0, 133.1, 130.6, 128.4, 127.4, 125.9, 117.1, 114.8, 114.4, 64.6, 48.5, 18.7.

LCMS $[M + H]^+$ m/z 239.

Typical procedure. T3P® (50% in EtOAc) (1 equiv., 0.5 mmol) was added to a solution of 2-aminobenzamide (**1a**, 0.5 mmol) and aldehyde (0.5 mmol) in acetonitrile (1 mL) in a sealed tube. After completion of the reaction (indicated by TLC, eluent CH_2Cl_2–MeOH 95/5), the precipitate formed was filtered, washed with cold acetonitrile (2 × 1 mL) and dried to afford the expected compound in sufficient purity.

2-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)benzonitrile (3f)

Yield: 116 mg (93% yield, white solid), m.p. (EtOH) 178–180 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.30 (br s, 1H), 7.92 (d, 1H, J = 7.6 Hz), 7.80–7.75 (m, 2H), 7.68 (dd, 1H, J = 7.6 Hz, 1.3 Hz), 7.63–7.59 (m, 1H), 7.31 (t, 1H, J = 7.6 Hz), 7.11 (br s, 1H), 6.77–6.72 (m, 2H), 6.07 (d, 1H, J = 2.3 Hz).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.3, 147.7, 143.3, 133.4, 133.3, 129.8, 128.6, 127.3, 117.7, 117.1, 114.6, 114.5, 110.9, 66.1.

LCMS $[M + H]^+$ m/z 250.

2-(Thiophen-3-yl)-2,3-dihydroquinazolin-4(1*H*)-one (3l)

Yield: 107 mg (93% yield, white powder), m.p. (EtOH) 191–193 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.33 (br s, 1H), 7.61 (d, 1H, J = 7.5 Hz), 7.52–7.50 (m, 1H), 7.46 (s, 1H), 7.26 (t, 1H, J = 7.5 Hz), 7.20 (d, 1H, J = 4.5 Hz), 7.12 (br s, 1H), 6.77 (d, 1H, J = 7.5 Hz), 6.69 (t, 1H, J = 7.5 Hz), 5.79 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.4, 147.7, 143.7, 133.2, 127.3, 126.7, 126.3, 123.0, 117.1, 115.0, 114.5, 62.5.

LCMS $[M + H]^+$ m/z 231.

2-(Thiazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (3m)

Yield: 109 mg (94% yield, white powder), m.p. (EtOH) 206–207 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.73 (br s, 1H), 7.77 (d, 1H, J = 2.8 Hz), 7.64–7.61 (m, 2H), 7.56 (br s, 1H), 7.28 (t, 1H, J = 7.3 Hz), 6.78 (d, 1H, J = 7.3 Hz), 6.72 (t, 1H, J = 7.3 Hz), 5.98 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 172.6, 162.6, 146.4, 142.4, 133.5, 127.3, 120.8, 117.7, 114.9, 114.8, 63.7.

LCMS $[M + H]^+$ m/z 232.

Acknowledgements

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