Synthesis of 3-Aryl-3,4-dihydro-4-hydroxy-4-phenylquinazoline-2-carbonitrile via 2-(Benzoyl)arylimino-4-chloro-5*H*-1,2,3-dithiazoles

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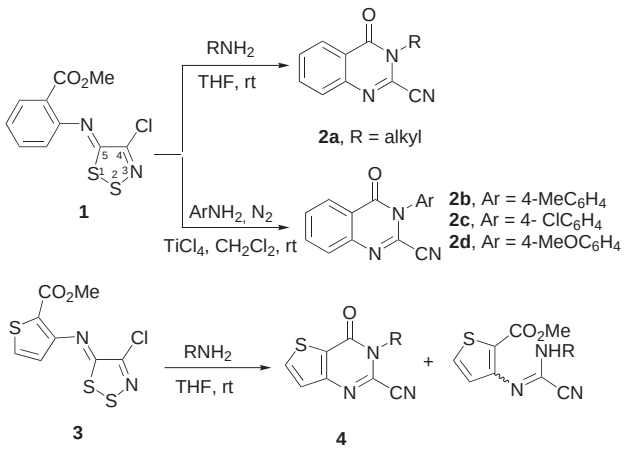
Abstract: Treatment of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazole-5-ylidene)anthranilate **1** with $TiCl_4$ (1.5 equiv.) in CH_2Cl_2 at r.t., followed by addition of arylamines gave quinazolin-4-ones **2** bearing an aryl group at position 3 in moderate yields. Similarly 4-hydroxy-4-phenylquinazolines **6** bearing an aryl group at position 3 were prepared in good to moderate yields from 2-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]benzophenones, **5**, $TiCl_4$, and arylamines under the same conditions. The ^{1}H NMR spectra of **6** in $CDCl_3$ indicate that the compounds exist as an equilibrium mixture of **6** and the corresponding ring-opened compound, *N*-(2-benzoylaryl)-2-cyanoamidines **7**. However, it is envisaged that compounds **6** exist as a single compound in a solid state in view of IR spectra showing no peak corresponding to a carbonyl absorption.

Key words: 1,2,3-dithiazoles, heterocycles, Lewis acid, quinazolines, titanium tetrachloride

Quinazolin-4-ones have received considerable attention owing to their variety of their biological activities such as antimalarial,[1] 5-HT_2 antagonist,[2] antitumor,[3] and tranquilizing effects,[4] etc., and numerous synthetic methods for creating the compounds have been developed.[5] In contrast, a limited number of synthetic methods have been reported for 4-hydroxyquinazolines although some 4-hydroxyquinazolines show activities such as inhibition of influenza virus,[6] stimulation of the growth of cobalamine requiring cultures by incorporation into the nucleotide of vitamin B_{12},[7] and hypoglycemic activity in normal fasted rats.[8] A survey of the literature shows that cyclization of 2-amidinobenzophenones, prepared from 2-benzoylanilides and hydrazine hydrate has been most widely used for the synthesis of 4-hydroxyquinazoline derivatives.[9] In addition, reactions of 2-aminobenzophenone alkylimines with acyl chlorides,[10] reactions of 2-acylaminobenzophenones with primary alkylamines,[10] the same reactions with hydrazine[9b] or ammonia,[11] and reaction of 2-(1-alkoxyethylideneamino)benzophenones with aminoacetaldehydes dialkyl acetals using on acid catalyst[12] have been utilized for the synthesis of 3,4-dihydro-4-hydroxy-4-phenylquinazolines. Grignard reagents are known to add across the carbonyl groups of *N*-substituted quinazolinones but are not generally a useful reaction because after addition an α–carbinolamines is formed that undergoes ring opening. However, the reaction of quinazoline-2,4-diones with arylmagnesium halides afforded 2,4-diaryl-4-hydroxyquinazolines.[13] There are other methods which lack general applicability. For example, 5-hydroxy-1-methyl-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline was prepared by the reaction of 1-methyl-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline with benzoyl peroxide in $CHCl_3$.[8] Treatment of 1-methylcarbamoylisatin with urea and thiourea[14] was reported to give 3,4-dihydro-4-hydroxy-3-methyl-4-ureidocarbonyl-2(1*H*)-quinazolinone and the corresponding sulfur analog, respectively. Dimerization of *N*-arylbenzimidoyl chloride in the presence of $ZnCl_2$, followed by addition of HCl afforded 3-aryl-3,4-dihydro-4-hydroxy-2,4-diphenylquinazolines.[15]

In connection with an ongoing project for exploring the synthetic utility of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles,[16] we reported previously the synthesis of 3-alkyl-2-cyanoquinazolin-4(3*H*)-ones **2a** and 3-alkyl-2-cyanothieno[3,2-*d*]pyrimidin-4(3*H*)-ones **4** by the reactions of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate **1** and methyl 3-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]-2-thiophenecarboxylate **3**, respectively with sterically less hindered primary alkylamines in THF at r.t. (Scheme 1).[17]



Scheme 1

However, neither compounds **1** nor **3** reacted with primary arylamines even at reflux temperature. The inertness of arylamines is understandable since compounds **1** and **3** were prepared by treatment of 4,5-dichloro-5*H*-1,2,3-dithiazolium chloride (Appel's salt) with arylamines in CH_2Cl_2 at r.t.[18]

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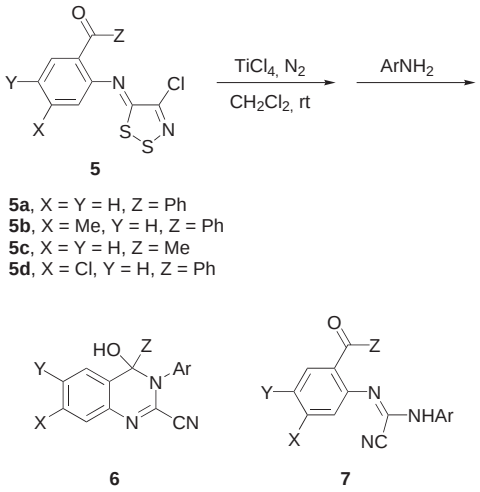
We intended to prepare quinazolinones having an aryl group at position 3 using readily available 5-arylimino-5*H*-1,2,3-dithiazole such as **1** as a starting material. Since the inertness of arylamines toward **1** was envisaged to be due to too weak nucleophilicity of arylamines, we tried to activate the nucleophilic center, i.e., C-5 of the 1,2,3-dithiazole ring by using a Lewis acid, which can interact with the non-bonding electrons on the carbonyl oxygen and the imino nitrogen atoms by forming a six-membered cyclic form. The results are described herein.

Treatment of **1** with a slight excess of $TiCl_4$ (1.5 equiv), followed by addition of excess primary arylamines (4 equiv) in CH_2Cl_2 under a nitrogen atmosphere at r.t. gave 3-aryl-2-cyanoquinazolin-4(3*H*)-ones **2b** (Ar = 4-MeC_6H_4) and **2c** (Ar = 4-ClC_6H_4) in 74% and 52% yields, respectively.[19] Application of the same methodology to 4- or 5-substituted 2-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]benzophenones **5** (Z = Ph), prepared from 4- or 5-substituted 2-aminobenzophenones and Appel's salt, gave white solids, which were recrystallized from a mixture of CH_2Cl_2 and *n*-hexane to give crystals **6** whose IR spectra did not exhibit the peaks corresponding to a carbonyl group.[20] Compounds **6** exist exclusively in this tautomeric form in the solid state. However, the ^1H NMR spectra of **6a**–**h** taken in $CDCl_3$ as a solvent indicate that the compounds exist as an equilibrium mixture of 3-aryl-3,4-dihydro-4-hydroxy-4-phenylquinazoline-2-carbonitriles **6** (Z = Ph) and the corresponding ring-opened compound **7**, *N*-(2-benzoylaryl)-2-cyanoamidines (Scheme 2).



5

5a, X = Y = H, Z = Ph
5b, X = Me, Y = H, Z = Ph
5c, X = Y = H, Z = Me
5d, X = Cl, Y = H, Z = Ph

6 **7**

Scheme 2

It was possible to determine which compound exists predominantly in $CDCl_3$ based on the absorptions corresponding to the OH protons of **6** and the NH protons of **7** exhibited at 4.78–6.79 and 11.23–11.47 ppm, respectively. In addition, the ratio of two compounds **6** and **7** could be determined based on the intensities of the proton signals of the group designated. Reaction time, yields and mp of the crystals and the ratios of **6** to **7** are summarized in the Table.

The Table shows that when the aryl group at position 3 has a substituent at the *para* position (entries 1, 2, 5, 7, and 8), **6** is predominantly formed except in the case of **6f**, which has a strong electron-withdrawing group, i.e., NO_2 (entry

Table Reaction Time, Yields, and Melting Points of Compounds **6**, and the Ratios of **6** to **7**

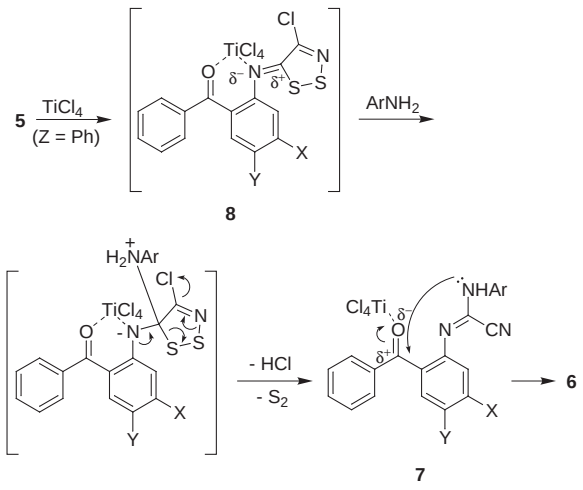
Entry	X	Y	Z	Ar	Time (h)	Yield[a]	Mp[b] (dec.) (°C)		Ratios in $CDCl_3$	^1H NMR (ppm)[c]		Basis
									(**6** : **7**)	**6**	**7**	
1	H	H	Ph	4-$MeOC_6H_4$	0.5	82	179–182	**a**	16.5:1.0	3.73 (s)	3.84 (s)	OCH_3
2	H	H	Ph	4-ClC_6H_4	2	63	166–168	**b**	1.6:1.0	7.73 (d)	7.67 (d)	ArH
3	Me	H	Ph	2-ClC_6H_4	13	70	176–178	**c**	1.0:2.6	2.20 (s)	2.45 (s)	CH_3
4	Me	H	Ph	3-ClC_6H_4	4	83	176–178	**d**	1.0:1.3	2.23 (s)	2.43 (s)	CH_3
5	Me	H	Ph	4-ClC_6H_4	4	71	176–178	**e**	1.3:1.0	2.23 (s)	2.44 (s)	CH_3
6	H	H	Ph	4-$O_2NC_6H_4$	20	74	138–140	**f**	1.0:3.7	8.27 (d)	8.07 (d)	ArH
7	Me	H	Ph	4-MeC_6H_4	0.5	58	191–193	**g**	4.1:1.0	2.24 (s)	2.39 (s) 2.45 (s)	CH_3[d]
8	Me	H	Ph	4-$MeOC_6H_4$	1	71	189–190	**h**	14.4:1.0	2.21 (s)	2.46 (s)	CH_3

[a] Isolated yields.
[b] Recrystallized from a mixture of CH_2Cl_2 and *n*-hexane.
[c] The spectra (300 MHz) were taken in $CDCl_3$ except for **6b** and **6e** (500 MHz) because of sparing solubilities of **6b** and **6e** in $CDCl_3$, s: singlet; d: doublet; m: multiplet.
[d] Two CH_3 groups of **6g** have identical chemical shift. In the case of **7g**, it was difficult to assign the chemical shifts of each methyl group because of their too close values.

6). In contrast, it appears that compound **7** is predominantly formed when the aryl group at position 3 has an *ortho* substituent (entry 3). The same trend is observed in the case of an *m*-substituted aryl group (entry 4). The predominant formation of **7c** over **6c** may be attributable to the steric effect by the presence of an *ortho* substituent in the Ar group, which hinders the intramolecular cyclization of **7** to give **6**. The slightly greater ratios of **7d** to **6d** (1.3:1.0, entry 4) might indicate the involvement of some kind of steric and electronic effects associated with *meta* substituent. The steric effects are expected to be completely free for a *para* substituted aryl group so that **6e** is predominantly formed (entry 5).

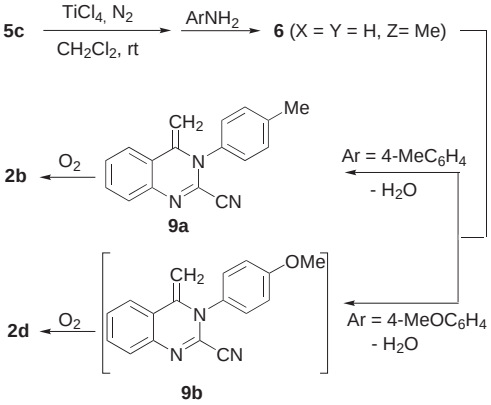
It is interesting to note that the ratios of **6** to **7** were decreased somewhat by the presence of a methyl group (X = Me) on the arylimino moiety despite Ar group being the same. For instance, the ratios of **6a** to **7a** which is 16.5:1.0 (entry 1) changed into 14.4:1.0 of **6h** to **7h** (entry 8) when Ar = 4-$MeOC_6H_4$. The same trend was observed in the case of Ar = 4-ClC_6H_4 (entries 2 and 5) despite triviality. This may be attributable to the high electron density on the carbonyl carbon due to the electron-donating effect of a methyl group so that nucleophilic attack by an arylamino group of **7** may be less favorable.

The mechanism for the formation of **6** may be rationalized based on the formation of the complex **8** in which $TiCl_4$ interacts with the nonbonding electrons on the carbonyl oxygen and the imino nitrogen at C-5 of 1,2,3-dithiazole moiety so that the imino carbon becomes a good nucleophilic center to react with arylamines, yielding eventually *N*-(2-benzoylaryl)-2-cyanoamidines **7**. Intramolecular cyclization of **7** in the presence of $TiCl_4$ affords **6** (Scheme 3).



Scheme 3

Similar treatment of 2-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]acetophenone **5c** with *p*-toluidine (3.5 equiv) in the presence of $TiCl_4$ (1.1 equiv) under the foregoing conditions for 11 h afforded, however, 4-methylenequinazoline **9a**[19] in 53% yield (Scheme 4). Compound **9a** underwent slow oxidation in the air to give **2b**[19] in 36% yield. On the other hand, the reaction with *p*-anisidine under similar conditions for 2 h, which is a shorter time than that for the reaction with *p*-toluidine gave **2d** in 58% yield. No **9b** analogous to **9a** was detected. The results suggest that compound **6** (X = Y = H, Z = Me) is formed as an intermediate, which eliminates rapidly a water molecule to give **9**. The methylene group of compound **9** is susceptible to air oxidation to give **2**. The result indicates that **9** is isolable depending on the substituent at position 3. Analogous air oxidation of the methylene group has been reported.[21]



Scheme 4

In conclusion, a synthetic method for quinazolin-4-ones **2** and 4-hydroxy-4-phenylquinazolines **6** bearing an aryl group at position 3 has been developed by treatment of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazole-5-ylidene)anthranilate **1** and 2-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]benzo- or acetophenones **5**, respectively, with $TiCl_4$ in CH_2Cl_2 under a nitrogen atmosphere at r.t., followed by addition of arylamines.

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(19) **General Procedure for the Synthesis of 3-Aryl-2-cyanoquinazolin-4(3*H*)-ones 2.** (A) To a solution of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilate (**1**) (0.42–0.94 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (0.82–1.37 mmol) by using a hypodermic syringe under nitrogen atmosphere. The solution turned immediately dark red. Arylamines (1.86–3.78 mmol) were added to the dark red solution, which was stirred until no spot corresponding to **1** was observed on TLC (silica gel, R_f = 0.6, EtOAc–hexane = 1:3). Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (25 mL × 3). The combined extracts were dried over $MgSO_4$, followed by evaporation of the solvent. The residue was chromatographed on a silica gel (70–230 mesh, 2 × 10 cm). Elution with *n*-hexane gave sulfur. Subsequent elution with a mixture of *n*-hexane and EtOAc (5:1) gave unknown mixtures and **2**. (B) To a solution of 2-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]acetophenone (**5c**) (0.36–0.59 mmol) in CH_2Cl_2 (15 mL) was added $TiCl_4$ (0.55–0.64 mmol) by using a hypodermic syringe under nitrogen atmosphere. Subsequently arylamines were added. When *p*-toluidine was added, the reaction mixture showed a yellow spot (R_f = 0.7, EtOAc–*n*-hexane = 1:3), assignable to be 3,4-dihydro-4-methylene-3-(4-tolyl)quinazoline-2-carbonitrile (**9a**). IR (neat): 2240, 1635, 1603, 1581, 1555, 1504, 1469, 1344, 1322, 1226, 1206, 1110, 816, 762 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.47 (s, 3 H, CH_3), 3.61 (d, 1 H, *J* = 2.5 Hz, =CH), 4.65 (d, 1 H, *J* = 2.5 Hz, =CH), 7.26–7.32 (m, 3 H, ArH), 7.36–7.52 (m, 4 H, ArH), 7.53 (d, 1 H, *J* = 7.8 Hz, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.8, 85.0, 112.1, 123.4, 123.7, 128.2, 128.9, 129.4, 131.1, 131.9, 133.1, 135.9, 140.8, 141.0, 142.8. Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.62; H, 5.09; N, 16.35. Compound **9a** gradually faded out during chromatography to give a new spot (R_f = 0.5, EtOAc–*n*-hexane = 1: 3), corresponding to 2-cyano-3-(4-tolyl)quinazolin-4(3*H*)-one (**2b**), which was eluted with a mixture of EtOAc and *n*-hexane (1:5) as an eluent to give **2b**, which was recrystallized from EtOH. Mp 175-176 °C. IR (KBr): 1677, 1581, 1501, 1456, 1328, 1312, 1274, 1104, 1082, 810, 774 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.49 (s, 3 H, CH_3), 7.31 (d, 2 H, *J* = 8.3 Hz, ArH), 7.43 (d, 2 H, *J* = 8.3 Hz, ArH), 7.67–7.73 (m, 1 H, ArH), 7.82–7.92 (m, 2 H, ArH), 8.38 (d, 1 H, *J* = 7.6 Hz, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.9, 111.6, 123.4, 127.9, 128.3, 129.1, 130.7, 131.2, 132.1, 132.9, 135.8, 141.5, 146.9, 160.6. Anal. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.50; H, 4.22; N, 16.21.
(20) **General Procedure for the Synthesis of 3-Aryl-3,4-dihydro-4-hydroxy-4-phenylquinazoline-4-carbonitriles 6.** To a solution of 2-[*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)]benzophenone (**5a**) (0.29–0.41 mmol) in CH_2Cl_2 (15 mL) was added $TiCl_4$ (0.46–0.91 mmol) by using a hypodermic syringe under nitrogen atmosphere, followed by addition of arylamines (0.61–1.03 mmol). The mixture was worked up as described in the general procedure for the synthesis of **2**. Elution with a mixture of *n*-hexane and EtOAc (3:1) gave **6a**,**b** and **6f**. 4-Hydroxy-3-(4-methoxyphenyl)-4-phenylquinazoline-2-carbonitrile (**6a**), which was recrystallized from a mixture of CH_2Cl_2 and *n*-hexane. Mp 179–182 °C (dec.). IR (KBr): 3168, 2224, 1597, 1578, 1454, 1467, 1446, 1354, 1290, 1248, 1168, 1030, 995, 819, 765, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.73 (s, 3 H, OCH_3 of major), 3.84 (s, 3 H, OCH_3 of minor), 5.99 (s, br, 1 H, OH of major), 6.60–6.66 (m, 2 H, ArH of major), 6.80–6.82 (m, 1 H ArH of major), 6.89 (d, 1 H, *J* = 7.4 Hz, ArH of major), 7.12–7.26 (m, 6 H, ArH of major), 7.39–7.53 (m, 2 H, ArH of major), 7.74–7.76 (m, 1 H, ArH of major). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.3, 87.6, 112.0, 113.7, 124.7, 127.6, 128.1, 128.1, 128.2, 128.3, 129.7, 129.8, 131.1, 133.1, 134.3, 139.0, 141.8, 159.7. The aromatic proton signals of minor compound are envisaged to overlap with those of major. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.49; H, 4.80; N, 11.71.
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