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SYNTHESIS OF 2-SUBSTITUTED AND 2,3-DISUBSTITUTED QUINAZOLIN-4-ONES CONTAINING A STERICALLY HINDERED PHENOL RESIDUE

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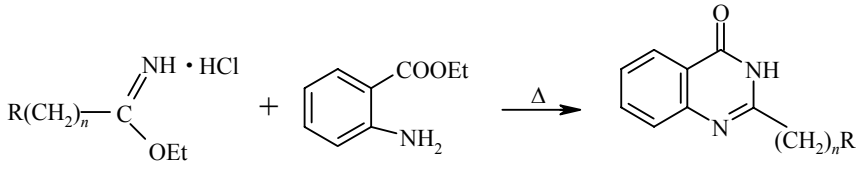
A series of 2-substituted and 2,3-disubstituted quinazolin-4-ones containing a 3,5-di(tert-butyl)-4-hydroxyphenyl group has been synthesized. They were prepared by the condensation of carboxylic acid imino ester hydrochlorides containing the indicated fragment with ethyl anthranilate and also by the reaction of azomethines, N-acylhydrazones, or the 4-phenylthiosemicarbazone of 3,5-di(tert-butyl)-4-hydroxybenzaldehyde with 2-methyl-4H-2,1-benzoxazin-4-one.

Keywords: azomethines, N-acylhydrazones, carboxylic acid imino esters, sterically hindered phenols, thiosemicarbazones, quinazolin-4-ones, condensation.

In this continuation of our study of the synthesis of five- and six-membered nitrogen containing heterocycles which include a shielded phenol residue [1-6] we report the preparation of 2-substituted and 2,3-disubstituted quinazolin-4-ones containing a 3,5-di(*tert*-butyl)-4-hydroxyphenyl group.

There is no information regarding the synthesis and properties of quinazolin-4-one derivatives which contain the indicated substituent. Compounds of this type are currently promising as potentially biologically active materials and also as stabilizers and additives to polymeric materials, hydrocarbon fuel, and lubricating oil.

Carboxylic acid imino esters hydrochlorides can be used as convenient synthons for the preparation of quinazolin-4-ones [7, 8]. In this work we have used as starting materials the ethyl imino ester hydrochlorides of 3,5-di(*tert*-butyl)-4-hydroxybenzoic (**1a**), 3,5-di(*tert*-butyl)-4-hydroxyphenylacetic (**1b**), β-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]propionic (**1c**), 3,5-di(*tert*-butyl)-4-hydroxyphenylthioacetic (**1d**), or β-[3,5-di(*tert*-butyl)-4-hydroxyphenylthio]propionic acid (**1e**). Condensation of the imino ester hydrochlorides **1a-e** with ethyl anthranilate gives the 2-substituted (3H)-quinazolin-4-ones **2a-e** containing the sterically hindered group.



1a–e **2a–e**

1, **2 a–c** R = 3,5-(*t*-Bu)$_2$–4-HOC$_6$H$_2$; **d**, **e** R = 3,5-(*t*-Bu)$_2$–4-HOC$_6$H$_2$S; **a** *n* = 0; **b**, **d** *n* = 1; **c**, **e** *n* = 2

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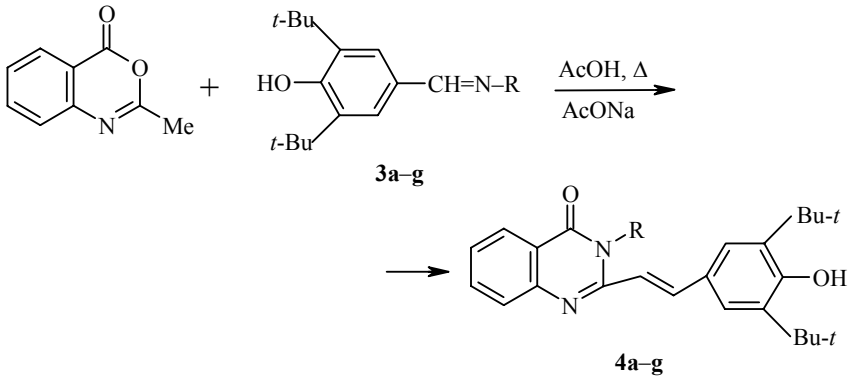
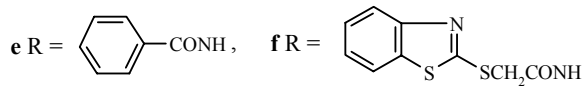
Improved yields of compounds **2a-e** (see Table 1) can be achieved by refluxing equimolar amounts of the reagents in ethanol or dioxane. It should be noted that the duration of the process depends on the reactivity of the starting imino ester hydrochlorides **1a-e**. Hence the formation of compounds **2b-e** is complete after refluxing the reagents in ethanol for 2.5-3 h whereas the preparation of the quinazolin-4-one **2a** from the imino ester hydrochloride **1a** needs refluxing in dioxane for 10 h, due to the effect of the electron-donor hydroxyaryl substituent [9] which is bonded to the imino ester group. Thin layer Al_2O_3 chromatography of the reaction products has shown that, in all of the examples except the quinazolin-4-ones **2a-e**, small amounts of the corresponding acid amides or nitriles were present in the reaction mixtures.

There is evidence that 2-methyl-4H-benzoxazin-4-one reacting with the aromatic aldehyde derivative azomethines in acetic acid in the presence of sodium acetate gives 3-substituted 2-styrylquinazolin-4-ones [7, 10-12].

In our work we decided to use this method for synthesizing quinazolin-4-ones containing the shielded phenol residue. With this in view we examined the reaction of 2-methyl-4H-3,1-benzoxazin-4-one with the N-alkyl(aryl, hetaryl)-3,5-di(*tert*-butyl)-4-hydroxybenzylideneamines **3a-d** and also with the N-acylhydrazones **3e,f** and 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde 4-phenylthiosemicarbazone (**3g**).



3, **4 a** R = C_8H_{17}, **b** R = 4-MeC_6H_4, **c** R = 2-pyridyl, **d** R = 2-thiazolyl, **g** R = PhNHCSNH,



It was found that refluxing equimolar amounts of the reagents and sodium acetate in acetic acid for 4-5 h gave 52-67% yields of the 2-[β-(3,5-di(*tert*-butyl)-4-hydroxyphenyl)vinyl]-3-R-quinazolin-4-ones **4a-g**. It should be noted that the azomethines and N-acylhydrazones which are derivatives of 3,5-di(*tert*-butyl)-4-hydroxyacetophenone do not react with 2-methyl-4H-3,1-benzoxazine under these conditions, the starting compounds being recovered unchanged from the reaction mixture even after heating in acetic acid in the presence of sodium acetate for 10 h.

The composition and structure of the synthesized quinazolin-4-ones **2a-e** and **4a-g** were confirmed by elemental analytical data and by IR and ^{1}H NMR spectroscopy. Hence the IR spectra of all of the compounds show a strong absorption in the region 1705-1680 cm^{-1} assigned to stretching vibrations of the carbonyl group ("amide 1" band) [7]. The C=N stretching vibration of the oxoquinazoline ring corresponds to the absorption band at 1625-1605 cm^{-1} whose intensity is almost as great as the C=O group absorption [7, 13]. Broad absorption bands are seen in the high frequency region of the spectra of the 2-substituted quinazolin-4-ones **2a-e** at 3360-3220 cm^{-1} and are assigned to the stretching vibrations of the NH group in the ring [7, 14]. The absorption bands of varying intensity in the range 1545-1525 cm^{-1} are associated with the planar deformation vibrations of the secondary amino NH groups.

TABLE 1. Parameters of the Quinazolin-4-one Derivatives **2a-e** and **4a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	R_f *[2]	^{1}H NMR spectrum, δ, ppm (J, Hz)*[3]	Yield, %
		C	H	N				
1	2	3	4	5	6	7	8	9
2a	$C_{22}H_{26}N_2O_2$	75.57 / 75.43	7.34 / 7.43	8.12 / 8.00	177-178	0.62	1.56 (18H, br. s, 2 *t*-C_4H_9); 4.97 (1H, s, HO); 7.25 (2H, s, H_{Ar}); 7.58-7.64 (4H, m, H_{Ar}); 9.37 (1H, br. s NH)	67
2b	$C_{23}H_{28}N_2O_2$	76.01 / 75.82	7.55 / 7.69	7.78 / 7.69	168-169	0.74	1.50 (18H, s, 2 *t*-C_4H_9); 3.34 (2H, s, RCH_2); 4.92 (1H, s, HO); 7.20 (2H, s, H_{Ar}); 7.60-7.67 (4H, m, H_{Ar}); 9.28 (1H, br. s NH)	76
2c	$C_{24}H_{30}N_2O_2$	76.06 / 76.19	8.07 / 7.94	7.58 / 7.40	128-129	0.82	1.52 (18H, s, 2 *t*-C_4H_9); 3.68-3.82 (4H, m, RCH_2CH_2); 5.05 (1H, s, HO), 7.24 (2H, s, H_{Ar}); 7.60-7.65 (4H, m, H_{Ar}); 9.35 (1H, br. s NH)	74
2d	$C_{23}H_{28}N_2O_2S$	69.57 / 69.70	7.01 / 7.07	7.21 / 7.07	184.0-184.5	0.70	1.54 (18H, s, 2 *t*-C_4H_9), 3.48 (2H, s, CH_2S), 5.12 (1H, s, HO), 7.30 (2H, s, $H_{arom.}$), 7.74-7.82 (4H, m, $H_{arom.}$), 9.48 (1H, br.s, NH)	81
2e	$C_{24}H_{30}N_2O_2S$	70.37 / 70.24	7.24 / 7.32	7.02 / 6.83	165-166	0.81	1.56 (18H, s, 2 *t*-C_4H_9); 2.98 (2H, br. s, CH_2S); 3.28 (2H, m, CH_2); 5.08 (1H, s, HO); 7.28 (2H, s, H_{Ar}); 7.58-7.64 (4H, m, H_{Ar}); 9.24 (1H, br. s NH)	72
4a	$C_{32}H_{44}N_2O_2$	78.87 / 78.65	8.96 / 9.17	5.60 / 5.73	89-91	0.70	1.12 (3H, t, CH_3); 2.52 (18H, s, 2 *t*-C_4H_9); 1.60-1.92 (12H, m, $6CH_2$); 3.64 (2H, m, CH_2N); 5.06 (1H, s, HO); 6.60 (1H, d, CH=CH, J = 16.0); 7.22 (2H, s, H_{Ar}); 7.30 (1H, d, J = 16.0, CH=CH); 7.72-7.80 (4H, m, H_{Ar})	52

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
4b	$C_{31}H_{34}N_2O_2$	80.02 79.83	7.37 7.30	5.83 6.01	111-113	0.54	1.58 (18H, br. s, 2 *t*-C_4H_9); 2.24 (3H, s, CH_3); 5.14 (1H, s, HO); 6.68 (1H, d, *J* = 16.8б CH=CH); 7.18-7.25 (6H, m, $2H_{Ar}$, $4H_{Het}$); 7.37 (1H, d, *J* = 16.8б CH=CH); 7.62-7.70 (4H, m, H_{Ar})	64
4c	$C_{29}H_{31}N_3O_2$	76.95 76.82	6.76 6.84	9.08 9.27	135-136	0.47	1.62 (18H, br. s, 2 *t*-C_4H_9); 4.96 (1H, s, HO); 6.72 (1H, d, *J* = 17.2, CH=CH); 7.20 (2H, s, H_{Ar}); 7.36 (1H, d, *J* = 17.2, CH=CH); 7.69-8.04 (8H, m, H_{Het})	58
4d	$C_{27}H_{29}N_3O_2S$	70.71 70.59	6.24 6.32	9.03 9.15	144-145	0.48	1.60 (18H, br. s, 2 *t*-C_4H_9); 5.18 (1H, s, HO); 6.65 (1H, d, *J* = 16.5, CH=CH); 6.94 (1H, d, J_{45} = 3.2, 5-H_{Het}); 7.20 (2H, s, H_{Ar}); 7.39 (1H, d, *J* = 16.5, CH=CH); 7.45 (1H, d, J_{45} = 3.2, 4-H_{Het}); 7.65-7.73 (4H, m, H_{Het})	65
4e	$C_{30}H_{32}N_4O_3$	72.70 72.58	6.33 6.45	11.41 11.29	128-129	0.32	1.54 (18H, br. s, 2 *t*-C_4H_9); 4.98 (1H, s, HO); 6.70 (1H, d, *J* = 17.0, CH=CH); 7.27 (2H, s, H_{Ar}); 7.36 (1H, d, *J* = 17.0, CH=CH); 7.58-7.82 (8H, m, H_{Het}); 8.78 (1H, br. s, NH)	60
4f	$C_{33}H_{34}N_4O_3S_2$	66.10 66.22	5.76 5.68	9.51 9.36	155-156	0.48	1.58 (18H, br. s, 2 *t*-C_4H_9); 3.84 (2H, s, CH_2S); 5.05 (1H, s, HO); 6.70 (1H, d, *J* = 16.8, CH=CH); 7.22 (2H, s, H_{Ar}); 7.34 (1H, d, *J* = 16.8, CH=CH); 7.58-7.74 (8H, m, H_{Het}); 9.08 (1H, br. s, NH)	62
4g	$C_{31}H_{34}N_4O_2S$	70.63 70.72	6.75 6.46	10.77 10.63	150.0-151.5	0.37	1.62 (18H, br. s, 2 *t*-C_4H_9); 5.04 (1H, s, HO); 6.36 (1H, br. s, NH); 6.60 (1H, d, *J* = 17.0, CH=CH); 6.76 (1H, br. s, NH); 6.92-7.02 (5H, m, H_{Ph}); 7.24 (2H, s, H_{Ar}); 7.35 (1H, d, *J* = 17.0, CH=CH); 7.70-7.87 (4H, m, H_{Het})	54

* Compounds **2a,b,4g** were recrystallized from 2-propanol; **2s,4d,f** from ethanol–water (1:1); **2d,e** from dioxane–toluene (1:1); **4b** from benzene; **4s,e** from ethanol–water (2:1).

*[2] Solvent system: chloroform–acetone, 50:1 (compounds **2a-s, 4e-g**); benzene–methanol, 30:1 (compounds **2d,e**); CCl_4–methanol, 15:1 (compounds **4a-d**).

*[3] Spectra of compounds **2a-e, 4e-g** were recorded in DMSO-d_6; compounds **4a-d** in $CDCl_3$.

The spectra of compounds **2a-e** taken in chloroform and dichloromethane show an absorption band shift for the C=O bond and the stretching vibrations of the NH group to higher frequency by 15-20 and 185-225 cm^{-1} respectively and the absorption band for the deformation of the NH group by 15-25 cm^{-1} to lower frequency and this may be connected with break up of intermolecular hydrogen bonds.

The spectra of the 2,3-disubstituted quinazolin-4-ones **4a-g** show two absorption bands of moderate intensity in the range 3125-3070 and 1670-1665 cm^{-1} and the intense absorption band at 980-975 cm^{-1} is characteristic of an α,β-disubstituted vinyl group with a trans configuration [15].

In all of the compounds discussed there is also observed an absorption which is due to the components of the sterically hindered phenol, *viz*. a rather narrow band at 3655-3635 (characteristic of a shielded phenolic hydroxyl [16]), two bands of medium intensity in the range 1260-1220 due to vibrations of the Ar–OH group in shielded phenols [17], and two groups of bands at 885-870 and 835-820 cm^{-1}(out of plane deformation vibrations of a tetra substituted benzene ring).

In the ^1H NMR spectra of the compounds synthesized (Table 1) the signal for the hydroxyl group appears as a singlet in the range 4.92-5.18 ppm, as seen in sterically hindered phenols [16, 18]. The signals for the *tert*-butyl protons are seen as a broadened singlet at 1.50-1.62 ppm The two magnetically equivalent protons in the hydroxyaryl component correspond to the singlet signal at 7.20-7.32 ppm [3, 4, 18].

In the spectra of the quinazolin-4-ones **2a-e** the signals for the NH group protons are found at 9.24-9.48 ppm, which is typical of such heterocycles [7, 13]. The spectra of the quinazolin-4-ones **4a-g** show the signals for the vinyl group protons as two doublets at 6.60-6.72 and 7.28-7.39 ppm with a spin-spin coupling of 16.0-17.2 Hz and this confirms the trans relationship of these protons [15]. The oxoquinazoline ring aromatic protons in the spectra of compounds **2a-e** and **4a-g** are seen as multiplet signals in the range 7.58-7.87 ppm.

EXPERIMENTAL

IR spectra were recorded on a Bruker IFS-48 instrument as KBr tablets, in vaseline oil, or in chloroform or dichloromethane. ^1H NMR spectra were taken on a Bruker WP-250 spectrometer (250 MHz) with TMS as internal standard. Monitoring of the course of the reaction and the purity of the compounds obtained was performed by TLC on Brockmann activity grade III Al_2O_3 and revealed using iodine vapor.

Parameters for the compounds synthesized are given in Table 1.

The starting ethylimino ester hydrochlorides **1a-e** [1], N-octyl- (**3a**) [19], N-(*p*-tolyl)- (**3b**) [20], N-(2-pyridyl)- (**3c**) and N-(2-thiazolyl)-3,5-di(*tert*-butyl)-4-hydroxybenzylideneamine (**3d**) [21] as well as N-(pyridyl-4-carbonyl)hydrazone (**3e**) [19], N-(benzothiazolyl-2-thioacetyl)hydrazone)**3f**) [22], and 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde 4-phenylthiosemicarbazone (**3g**) [21] were prepared by the known methods quoted individually above.

2-Substituted (3H)-quinazolin-4-ones (2a-e). A mixture of the ethylimino ester hydrochloride **1a-e** (15 mmol) and ethyl anthranilate (2.47 g, 15 mmol) was refluxed with stirring for 10 h in 40 ml of anhydrous dioxane (for the preparation of compound **2a**) or for 3 h in absolute ethanol (for compounds **2b-e**). The reaction mixture was evaporated to dryness at reduced pressure and the residue was crystallized from the appropriate solvent.

2-[β-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)vinyl]-3-R-(3H)-quinazolin-4-ones (4a-g). A mixture of 10 mmol of the azomethine **3a-d**, N-acylhydrazone **3e,f**, or 4-phenylthiosemicarbazone **3g** with 2-methyl-4H-2,1-benzoxazin-4-one (1.49 g, 10 mmol), and sodium acetate (0.82 g, 10 mmol) in acetic acid (45 ml) was refluxed with stirring for 5 h, cooled to 20°C, and poured into iced water (200 ml). The precipitated solid was filtered off, washed on the filter with water, dried, and either crystallized from the appropriate solvent (see Table 1) or chromatographed on an L 100/160 micron silica gel column (h = 50 cm, d = 4.5 cm) (for the preparation of compound **4a**) using chloroform as eluent.

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