SYNTHESIS OF 1,3-DISUBSTITUTED 1,2,4-TRIAZOLO[4,3-*a*]QUINAZOLIN-5-ONE DERIVATIVES

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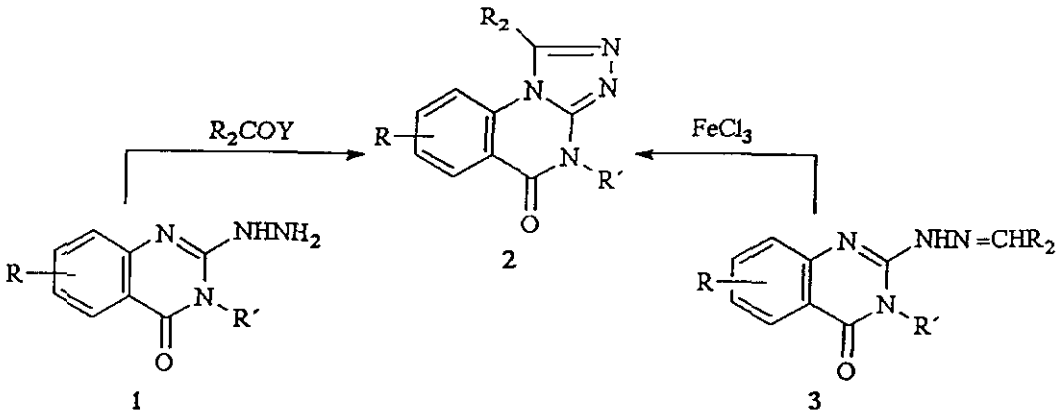
Abstract - Treatment of hydrazonoyl halides 8 with 2-mercapto-4(3*H*)-quinazolinone (7) in refluxing chloroform in the presence of triethylamine afforded 1,3-disubstituted 1,2,4-triazolo[4,3-*a*]quinazolin-5-one derivatives.

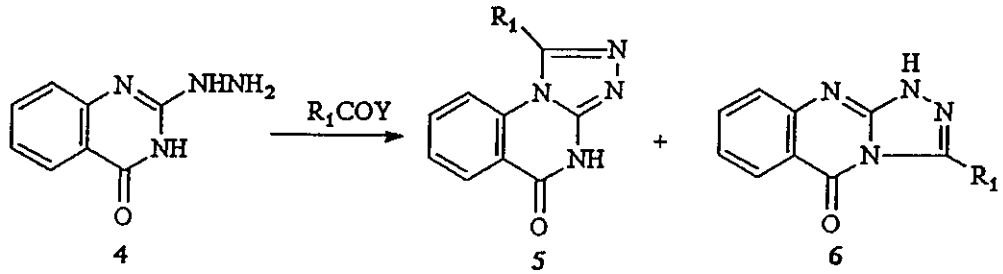
Literature routes, applicable to the synthesis of 1,2,4-triazolo[4,3-*a*]quinazolin-5-ones (2), have so far been confined to the cyclization reaction of 2-hydrazino 3-substituted quinazolin-4-one[1,2] (1) with carboxylic acids or their derivatives or oxidative cyclization of hydrazones (3), derived from 3-substituted 2-hydrazinoquinazolin-4-one and aromatic aldehydes, with ferric chloride.[3,4] Cyclization of 3-unsubstituted 2-hydrazinoquinazolin-4-one[4] (4) with



carboxylic acids or their derivatives led to the formation of a mixture of the angular 1,2,4-triazolo[4,3-*a*]quinazolin-5-one (5) and the linear 1,2,4-triazolo[3,4-*b*]quinazolin-5-one (6).

In this paper, we introduce one-pot synthesis for the title compounds (13) utilizes readily inexpensive reactants and gives good yields. Also, it provides direct access to a variety of

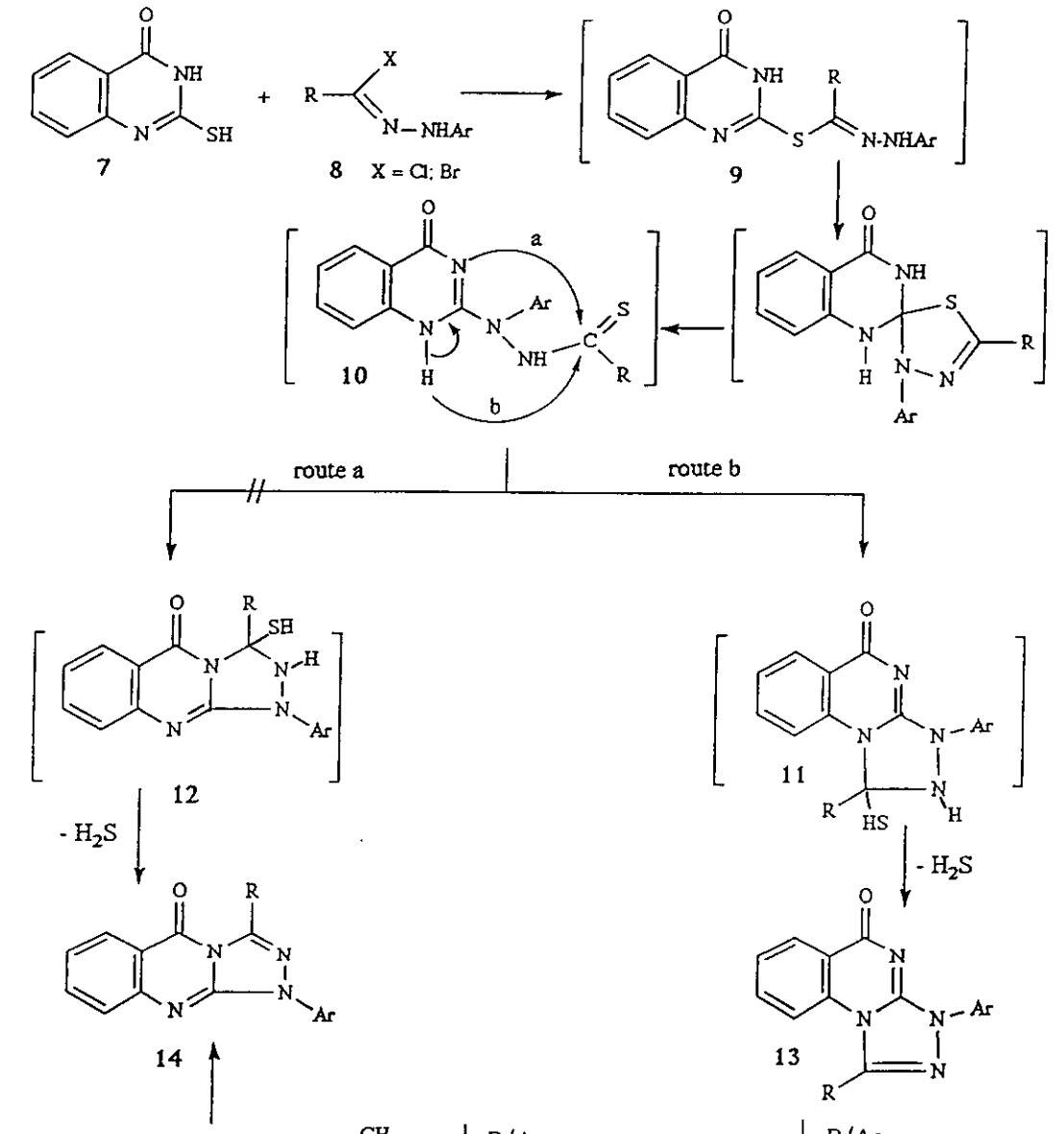
substituents at N-1 and C-3 heteroring positions. Evidently, this route is of wide scope and generality so that it competes favourably with the methods reported for the preparation of 1,2,4-triazolo[4,3-*a*]quinazolin-5-one derivatives.



4 5 6

The starting 2-mercapto-4(3*H*)quinazolinone (7) was prepared according to the reported procedure.[5] The reaction of hydrazonoyl halides (8) with **7** were carried out in refluxing chloroform in the presence of triethylamine for few hours till hydrogen sulfide gas ceased to evolve. After concentration of the reaction mixture, 1,2,4-triazolo[4,3-*a*]quinazolin-5-ones were formed (Scheme 1). All the reactions examined are regioselective and in all cases only one of the isomeric structures (13) or (14) has been isolated. The formation of one isomer is also evidenced on the basis of tlc and ^{1}H nmr spectrometry of the crude reaction mixtures.

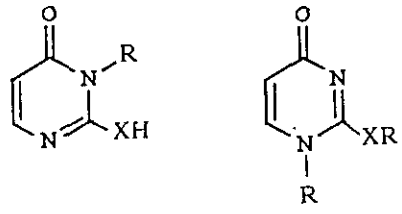
The reaction pathway that seems to account for the formation of **13** from **8** and **7** is outlined in Scheme 1. It is proposed that the reaction involves an initial nucleophilic substitution to give thiohydrazonate esters (9), which undergo S → N heteroaryl migration to give the thiohydrazides (10). In the final stage of the reactions, the intermediate thiohydrazides (10) undergo cyclization with concurrent elimination of hydrogen sulfide to give the final product. In these reactions there seem to be two possible courses for the cyclization of **10** to give **13** or **14** depending on the direction of the cyclization (a and or b in Scheme 1). In the intermediate, thiohydrazide (10), the less nucleophilic nitrogen N-3 due to electronic effect of the carbonyl group[6,7] could cause preferential ring closure to 1,3-disubstituted 1,2,4-triazolo[4,3-*a*]quinazolin-5-one (13). Moreover, the structures of the products (13) were further substantiated by comparison with authentic samples of their regioisomers (14). For example, the ir spectrum of **14a**, prepared from 1-(*p*-nitrophenyl)-3-methyl-1,2,4-triazol-5-one with anthranilic acid according to literature method,[8] was found diff-



	R/Ar		R/Ar
a	$CH_3/p\text{-}NO_2C_6H_4$	h	C_6H_5CO/C_6H_5
b	$CH_3CH_2/p\text{-}NO_2C_6H_4$	i	2-thienoyl/C_6H_5
c	C_6H_5/C_6H_5	j	$C_6H_5/p\text{-}NO_2C_6H_4$
d	$C_6H_5CH{=}CH/C_6H_5$	k	2-naphthoyl/C_6H_5
e	2-thienyl/$p\text{-}NO_2C_6H_4$	l	2-furyl/$p\text{-}NO_2C_6H_4$
f	CH_3CO/C_6H_5	m	C_6H_5NHCO/C_6H_5
g	C_2H_5OCO/C_6H_5		

Scheme 1

rent from 13a *and its melting point with* 13a showed depression. Also, 13a exhibits its absorption maximum at λ 327 nm whereas its isomer 14a shows its maximum at λ 379 nm. This difference is in agreement with the fact that absorption maxima of quinones of type 15a are known to be lie at shorter wavelength than those of the dienones 15b.[9]



15a 15b

X = NH

The structural assignment of the isolated products (13) is confirmed from their analytical and spectral data (ir, ^{1}H-nmr, ms) (experimental). On the basis of these findings the products isolated from the studied reactions were assigned structure (13).

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were recorded on a Pye Unicam Sp-300 IR spectrophotometer. ^{1}H Nmr spectra were recorded on a Varian Gemini 200 and Varian EM 390 spectrometers for solution in deuterated chloroform or dimethyl sulfoxide-d_6 using tetramethylsilane as internal standard. Mass spectra were recorded on a GCMS-QP 1000-EX Shimadzu, Japan. Elemental analyses were performed by the microanalytical laboratory, University of Cairo, Giza, Egypt. The hydrazonoyl halides (8a),[10] (8b),[10] (8c),[11] (8d),[12] (8e),[13] (8f),[14] (8g),[15] (8h),[16] (8i),[17] (8j),[18] (8k),[19] (8l),[20] and (8m)[21] were prepared as previously described.

General method for preparation of 1,3-disubstituted 1,2,4-triazolo[4,3-*a*]quinazolin-5-ones (13). To a stirred solution of the appropriate hydrazonoyl halides (8) (5 mmol) and 2-mercapto-4(3*H*)-quinazolinone (7) (0.9 g, 5 mmol) in chloroform (40 ml) was added triethylamine (0.7 ml, 5 mmol) at room temperature. The reaction mixture was refluxed till hydrogen sulfide ceased to evolve (10-12 h). The reaction mixture was washed three times with water and the organic layer was collected, dried over anhydrous sodium sulfate and then filtered. The solvent was evaporated under reduced pressure and the residue was treated with methanol. The solid was collected and crystallized from suitable solvent to

give the corresponding 1,2,4-triazolo[4,3-a]quinazolin-5-one derivatives (**13a-m**).

13a: mp 220-222°C (DMF); yield 1.13 g (71 %); δ ($CDCl_3$) 2.4 (s, 3H), 7.0-8.6 (m, 8H) ppm; υ (KBr) 1709 (C=O) cm^{-1}; ms m/z 321, 275, 206, 130, 102, 90, 77. Anal. Calcd for $C_{16}H_{11}N_5O_3$: C, 59.8; H, 3.4; N, 21.8. Found: C, 59.8; H, 3.5; N, 21.5.

13b: mp 223-224°C (acetic acid); yield 1.17 g (70 %); δ ($CDCl_3$) 1.2 (t, J = 7 Hz, 3H), 2.2 (q, J = 7 Hz, 2H), 7.0-8.5 (m, 8H) ppm; υ (KBr) 1710 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_5O_3$: C, 60.7; H, 3.9; N, 20.9. Found: C, 60.9; H, 3.9; N, 20.6.

13c: mp 240-242°C (acetic acid); yield 1.27 g (75 %); δ ($CDCl_3$) 7.2-8.0 (m, Ar-H) ppm; υ (KBr) 1700 (C=O) cm^{-1}; ms m/z 338, 233, 206, 130, 102, 91, 77, 51. Anal. Calcd for $C_{21}H_{14}N_4O$: C, 74.5; H, 4.1; N, 16.5. Found: C, 74.3; H, 4.2; N, 16.3.

13d: mp 214-215°C (acetic acid); yield 1.27 g (70 %); δ ($CDCl_3$) 7.2-8.4 (m, Ar-H) ppm; υ (KBr) 1710 (C=O) cm^{-1}; ms m/z 364, 287, 236, 182, 130, 102, 91, 77, 51. Anal. Calcd for $C_{23}H_{16}N_4O$: C, 75.8; H, 4.4; N, 15.4. Found: C, 75.6; H, 4.1; N, 15.2.

13e: mp 258-260°C (benzene); yield 1.17 g (60 %); δ ($CDCl_3$) 6.9-8.3 (m, Ar-H) ppm; υ (KBr) 1710 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{11}N_5O_3S$: C, 58.6; H, 2.8; N, 18.0. Found: C, 58.7; H, 2.6; N, 17.8.

13f: mp 170°C (ethanol); yield 0.99 g (65 %); δ ($CDCl_3$) 2.9 (s, 3H), 7.2-8.4 (m, 9H) ppm; υ (KBr) 1730 (C=O), 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{12}N_4O_2$: C, 67.1; H, 4.0; N, 18.4. Found: C, 67.3; H, 3.9; N, 18.1.

13g: mp 156°C (ethanol); yield 1.12 g (67 %); δ ($CDCl_3$) 1.5 (t, J = 7 Hz, 3H), 4.6 (q, J = 7 Hz, 2H), 7.3-8.4 (m, 9H) ppm; υ (KBr) 1760 (C=O), 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.7; H, 4.2; N, 16.6. Found: C, 65.0; H, 4.3; N, 16.5.

13h: mp 226-228°C (acetic acid); yield 1.19 g (65 %); δ ($CDCl_3$) 7.0-8.2 (m, Ar-H) ppm; υ (KBr) 1710 (C=O), 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{14}N_4O_2$: C, 72.1; H, 3.9; N, 15.0. Found: C, 72.6; H, 3.3; N, 15.0.

13i: mp 244-246°C (acetic acid); yield 1.26 g (68 %); δ (DMSO-d_6) 7.0-8.0 (m, Ar-H) ppm; υ (KBr) 1710 (C=O), 1660 (C=O) cm^{-1}; ms m/z 372, 261, 186, 166, 111, 90, 77, 51. Anal. Calcd for $C_{20}H_{12}N_4O_2S$: C, 64.5; H, 3.2; N, 15.0. Found: C, 64.2; H, 3.4; N, 14.7.

13j: mp 268-270°C (acetic acid); yield 1.44 g (75 %); δ (DMSO-d_6) 6.8-8.5 (m, Ar-H) ppm; υ (KBr) 1700 (C=O) cm^{-1}; ms m/z 383, 337, 234, 206, 169, 130, 102, 90, 77, 51.

Anal. Calcd for $C_{21}H_{13}N_5O_3$: C, 65.8; H, 3.4; N, 18.3. Found: C, 65.5; H, 3.4; N, 18.3.

13k: mp 243-245°C (dioxane); yield 1.49 g (72 %); δ (DMSO-d_6) 7.1-8.6 (m, 15H), 9.1 (s, 1H) ppm; υ (KBr) 1720 (C=O), 1650 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{16}N_4O_2$: C, 75.0; H, 3.8; N, 13.4. Found: C, 74.8; H, 3.6; N, 13.2.

13l: mp 250-252°C (DMF); yield 1.30 g (70 %); δ (DMSO-d_6) 6.8-8.5 (m, Ar-H) ppm; υ (KBr) 1710 (C=O) cm^{-1}; ms m/z 373, 343, 266, 234, 218, 177, 169, 130, 118, 102, 90, 77, 51. Anal. Calcd for $C_{19}H_{11}N_5O_4$: C, 61.0; H, 2.9; N, 18.7. Found: C, 60.7; H, 3.2; N, 18.5.

13m: mp 245-247°C (acetic acid); yield 1.43 g (75 %); δ (DMSO-d_6) 7.0 – 8.6 (m, Ar-H) ppm; υ (KBr) 3350 (NH), 1710 (C=O), 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{15}N_5O_2$: C, 69.3; H, 3.9; N, 18.4. Found: C, 69.5; H, 4.2; N, 18.1.

Preparation of 1-(*p*-nitrophenyl)-3-methyl-1,2,4-triazolo[3,4-*b*]quinazolin-5-one 14a. A mixture of 1-(*p*-nitrophenyl)-3-methyl-4,5-dihydro-1,2,4-triazol-5-one (4.5 g, 20 mmol), anthranilic acid (3.0 g, 20 mmol) and phosphorus trichloride (30 ml) was heated under reflux for 4 h. The excess phosphorus trichloride was distilled off and the residue was washed with sodium hydroxide (10 %) and finally with water. The solid formed was crystallized from ethanol to give **14a**, mp 293°C [Lit. mp 293°C].[8]

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