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Substituted quinolinones. 20. Synthesis of some new 3-heterocyclic quinolinones using *E*-3-(3-(dimethylamino)-acryloyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one

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ABSTRACT

Treatment of *E*-3-(3-(dimethylamino)acryloyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one with glacial acetic acid and/or thionyl chloride afforded pyrano[3,2-*c*]quinoline-4,5-diones while its a-electrophilic substitution reactions with allyl isothiocyanate and *p*-nitrobenezenediazonium chloride furnished the N-allylthioamide and arylazo-enol derivatives. The latter arylazo-enol derivative was subjected to heterocyclization some active methylene esters affording new pyrazole and pyridazine derivatives. The reaction of the titled enaminone with some 1,2-, 1,3-, and 1,4-binucleophilic reagents led to formation of novel quinolinones bearing various five-, six, and seven-membered heterocyclic substituents at position-3.

KEYWORDS

Quinolin-2(1H)-one;
β-enaminone;
Pyrano[3,2-c]quinoline-4,5-dione;
Azoles;
Azines;
Azepines.

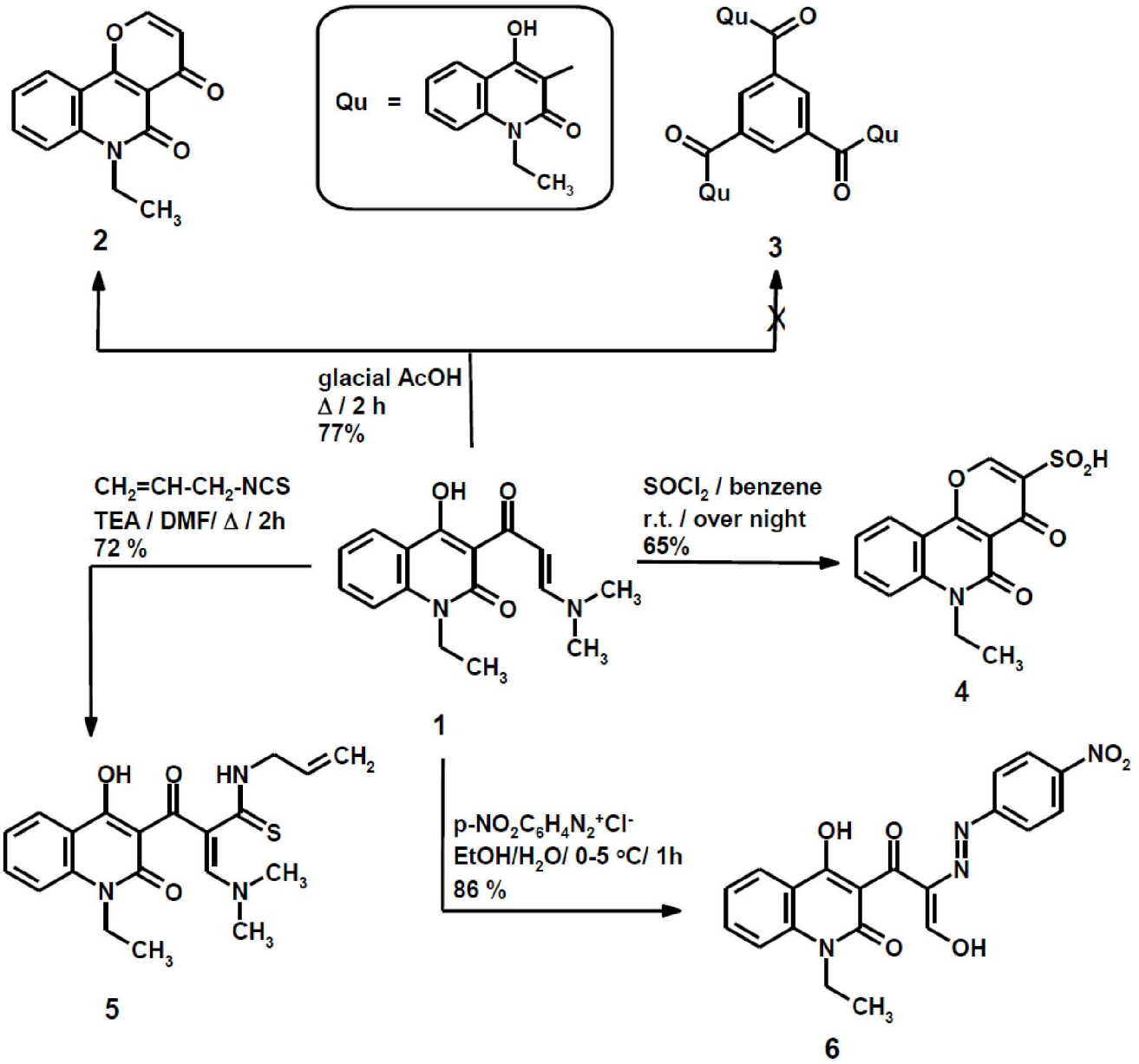
INTRODUCTION

Quinolines in general and quinolinones in particular represent a family of the most active classes of heterocyclic compounds possessing a wide variety of significant medicinal, pharmacological and industrial applications[1–4]. With more than 800 million patients treated, quinolinones are currently one of the main classes of agent in the antimicrobial armamentarium, with therapeutic indications having evolved from urinary tract infections in the early 1970s to infections of almost all body compartments at the present time[5]. On the other hand, β-enaminone derivatives of quinolinone were found as widespread building blocks in heterocyclic synthesis of interesting antiparasitic agents[6-9]. Thus, the versatile chemical properties of β-enaminone system towards some electrophilic and nucleophilic reagents[10] evoked our attention to utilize *E*-3-(3-(dimethylamino)acryloyl)-1-ethyl-4-hydroxyquinolin-2(1H)-one as starting material to explore and synthesize some new heterocyclic systems as substituents at position-3 of quinolinone of expected antiparasitic activity.

RESULTS AND DISCUSSION

(E)-3-(3-(Dimethylamino)acryloyl)-1-ethyl-4-hydroxyquinolin-2(1H)-one **(1)** was obtained via the condensation reaction of 3-acetyl-1-ethyl-4-hydroxyquinolin-2(1*H*)-one with dimethylformamide dimethylacetal (DMF-DMA), as previously described[1]. It was reported that when β-enaminones were treated with boiling acetic acid, electrophilic trimerization took place leading to 1,3,5-triacylbenzene

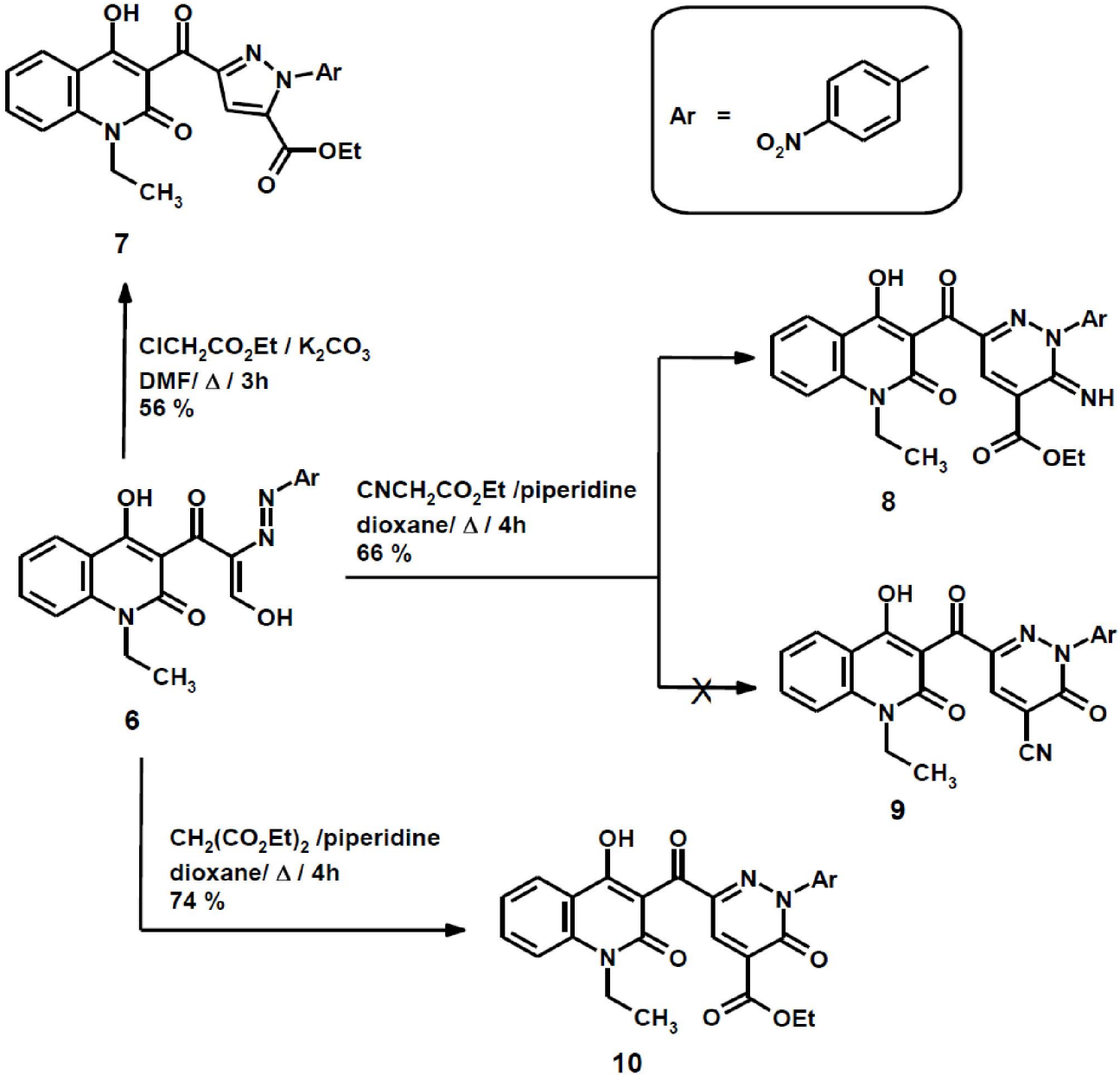
derivatives[11]. Hence, the enaminone **(1)** was boiled in glacial acetic acid. Characterization of the product showed that an intramolecular ring closure occurred to give 6-ethylpyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (**2**) instead the expected 1,3,5-triacylbenzene derivative **(3)** (Scheme 1). IR spectrum of the pyranoquinolinedione **(2)** showed absorption band at n 1670 cm^{-1} (C=O) due to pyranone, and 1640 cm^{-1} (C=O) due to quinolone. ^{1}H NMR spectrum showed the presence of characteristic αH-pyran-4-one proton, as doublet at δ = 9.01. Treatment of the enaminone **(1)** with thionyl chloride, in dry benzene, afforded the angular tricyclic system; 6-ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-sulfinic acid **(4)**, in good yield. ^{1}H NMR spectrum of compound **(4)** confirmed the existence of an acidic group (SO_2H), which appeared as a broad singlet at δ 14.82 and αH-pyarn-4-one proton that appeared as singlet at δ 9.20. These results confirmed existence of a similar intramolecular cyclization accompanied by sulfination (Scheme 1).



Scheme 1 : Some electrophilic reactions with the enaminone (1)

The electrophilic reaction of allyl isothiocyanate with the enaminone **(1)**, in presence of triethylamine, afforded the N-allylpropenethioamide **(5)** (Scheme 1). In addition to elemental analysis, structure evidences

of which were gained from the ^{1}H NMR spectrum which revealed the specific signal sets of the N-allyl and dimethylaminomethylene groups (TABLE 1). The enaminone **(1)** was smoothly coupled with 4-nitrobenzenediazonium chloride to yield the corresponding arylazo-enol **(6)**, in good yield (Scheme 1). Analytical data of the product **(6)** revealed the hydrolysis of dimethylamino group of the enaminone system, during the course of reaction. ^{1}H NMR spectrum (DMSO-d_6) indicated that in solution the product **(6)** exists mainly in the α-arylazo-enol form. Thus, two specific signals were observed at δ 6.35 and 8.58 (exchangeable with D_2O) due to enolic C=C*H*–O*H*. Oppositely, IR spectrum (KBr) showed the predominance of the α-hydrazone-aldehyde form in the solid state. In addition, IR spectrum confirmed the existence of characteristic band due to H-bonded N–H and O–H groups at ν 3285–3100 cm^{-1} and stretching band characteristic for formyl group (CH=O) appeared at ν 1661 cm^{-1} (TABLE 1). These findings lead to conclude that the product **(6)** exists in tautomerism in which azo-enolic form predominates in solution state while hydrazono-aldehydic form predominates in solid state.



Scheme 2 : Some cyclization reactions with the hydrazonopropanal derivative (6)

The arylazo-enol **(6)** reacted with ethyl chloroacetate, in presence of potassium carbonate, to give the ethyl 1,3-disubstituted pyrazole-5-carboxylate **(7)** (Scheme 2). The ^{1}H NMR spectrum of compound **(7)** revealed the presence of nine benzo-protons due to quinoline 1,4-disubstituted benzene, and 4-H of pyrazole. In addition ^{1}H NMR spectrum showed the presence of chemical shift signals due two protons sets of both *N*-ethyl and *O*-ethyl groups. IR spectrum fortified the proposed orientation of heterocyclization showing existence of strong absorption bands at ν 1744, 1675, and 1636 cm^{-1} due to carbonyl functions of ester, ketone, and quinoline-2-one moieties, respectively.

Treatment of the arylazo-enol **(6)** with ethyl cyanoacetate, in presence of piperidine, produced ethyl 1,3-disubstituted 6-iminopyridazine-5-carboxylate **(8)** (Scheme 2). Exclusion of formation of the possible 6-oxopyridazine-5-carbonitrile **(9)** was based on the presence of a typical carboxylate function was observed at ν = 1720 cm^{-1} and absence of specific C≡N stretching band in IR spectrum of the product. ^{1}H NMR spectrum showed the existence of both *N*-ethyl and *O*-ethyl set of protons. Moreover, the presence of broad singlet proton at δ = 9.21 due to an imino (N–H) (TABLE 1).

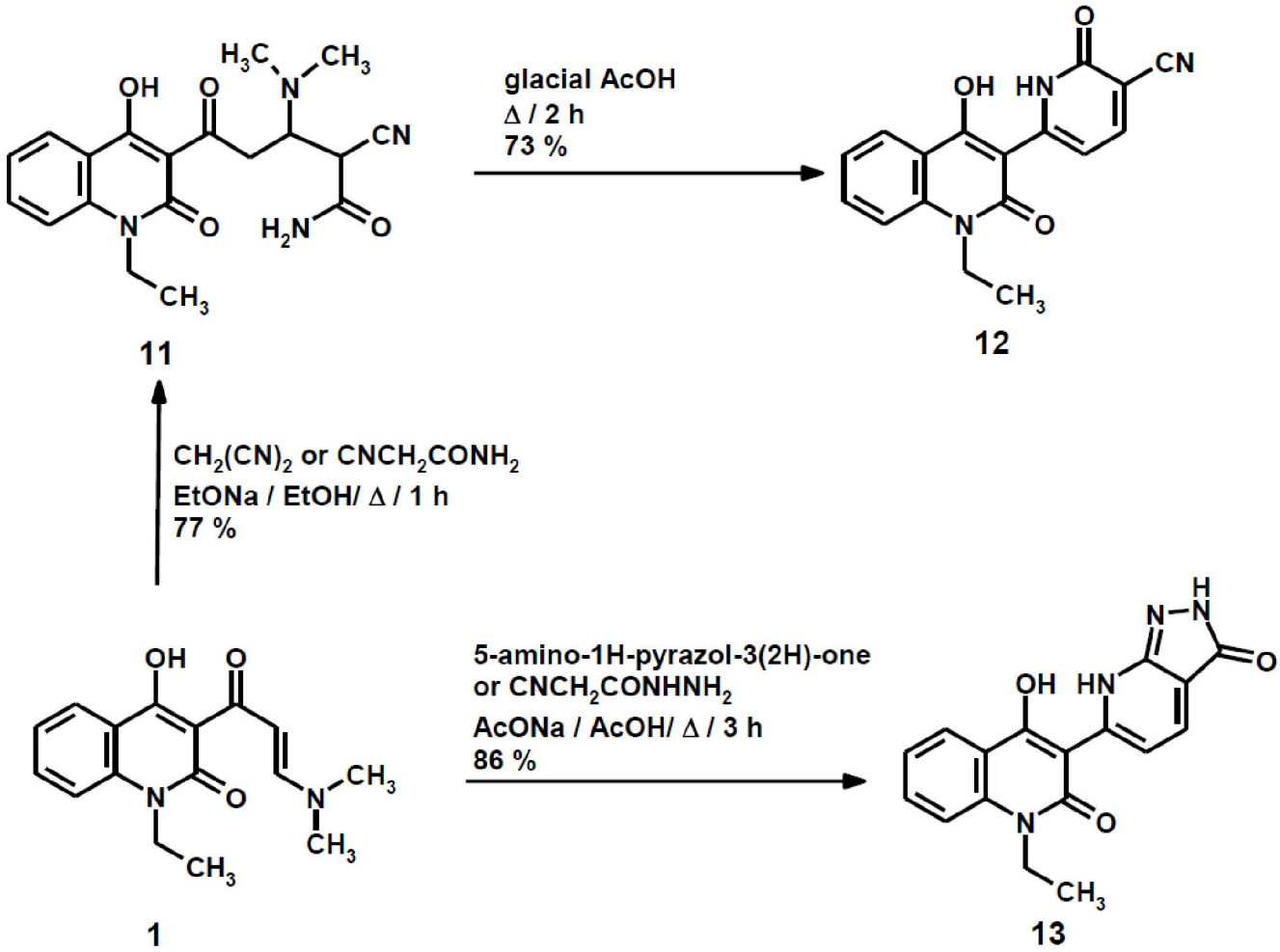
The reaction of the arylazo-enol **(6)** with diethyl malonate furnished ethyl 1,3-disubstituted 6-oxopyridazine-5-carboxylate **(10)** (Scheme 2). IR spectrum of the pyridazinone **(10)** showed specific absorption bonds at ν 1748 and 1705, 1675, 1626 cm^{-1} due to carbonyl functions of ester, pyridazine-6-one, ketone, and quinolin-2-one moieties, respectively. ^{1}H NMR spectrum of the pyridazinone **(10)** showed the presence of chemical shift signals due two protons sets of both *N*-ethyl and *O*-ethyl groups (TABLE 1).

When the enaminone **(1)** was subjected to react with malononitrile, in presence of sodium ethoxide, the adduct; 5-oxopentamide **(11)** was obtained (Scheme 3). The mass spectrum of the amide **(11)** showed peak at m/z (*I* %): 370 (6.13) due to molecular ion (M^+, $C_{19}H_{22}N_4O_4\varepsilon^+$). IR spectrum of the amide **(11)** exhibited stretching vibrational bands at ν 4520, 3389, 3273 cm^{-1} due to O–H and amide NH_2, and 2225 cm^{-1} due to C≡N. In addition to three different absorption bands at ν 1685, 1678, and 1644 cm^{-1} due to (C=O) functions of amide, ketone, and quinolin-2-one moieties, respectively (TABLE 1). Moreover, ^{1}H NMR spectrum revealed the presence of the chemical shifts distinguishing the aliphatic chain (COC*H*$_2$C*H* (NMe$_2$)C*H* (CN)CONH$_2$), beside two singlets of *N*,*N*-dimethyl group and NH_2 protons. Building on these results, two observations on the structure of the adduct **(11)** are noted; (i) the dimethylamine is not eliminated as usual, (ii) partial hydrolysis of one of the two carbonitrile groups took place. In consequence of these results it was thought that the reaction proceeded via *Michael* addition and a consequent acid hydrolysis of a carbonitrile group to a carboxamide one might take place during work-up. Furthermore preparative verification of structure of the amide **(11)** was achieved through obtaining the same product by the addition reaction of cyanoacetamide with the enaminone **(1),** under similar reaction conditions (Scheme 3). Intramolecular heterocyclization of the amide **(11)** was smoothly achieved, in boiling glacial acetic acid, giving the 3-(pyidin-2-yl)quinolinone derivative **(12)** (Scheme 3). ^{1}H NMR spectrum presented signals specific for chemical shifts of β- and γ-protons of pyridine exist within the aromatic region at δ 7.33–8.07 and the proton of (O=C–N–H ↔ H–O–C=N) of a-pyridone moiety, as broad singlet at δ 13.41 nearby chemical shift at δ 13.93 of O–H of 4-hydroxyquinoline.

Interestingly, the reaction of the enaminone **(1)** with the commercially available 3-amino-5-hydroxy-1*H*-pyrazole or cyanoacetohydrazide gave the same product **(13)** (Scheme 3). The structure of the product; pyrazolo[3,4-b]pyridine derivative **(13)** was established, on basis of analytical and spectral results. In ^{1}H NMR, it is observed that the γ-proton at of pyridine be influenced by anisotropic effect of C=O, causing the observed more downfield shift to d 8.45. Besides, two singlet peaks were seen at δ 9.99 and 10.29 owing to two N–H groups (TABLE 1).

The enaminone **(1)** was subjected to react with hydrazine hydrate[12], to afford the 1*H*-pyrazole derivative **(14)** (Scheme 4). It was stated that there is a rapid equilibrium in 5-substituted 1*H*-pyrazole to its tautomer; 3-substituted 1*H*-pyrazole[13]. ^{1}H NMR spectrum (DMSO-d_6) of the product showed the appearance of N–H signal at a relatively more downfield chemical shift (δ 13.42) than the normal chemical shift of similar heteroaromatic N–H. This result suggest the presence

of strong hydrogen-bonding (C=O···H–N) which leads to structure fixation. Hence, as a result, this diminishes fast equilibration between the two tuatomers and the 5-substituted 1*H*-pyrazole tautomer predominates.



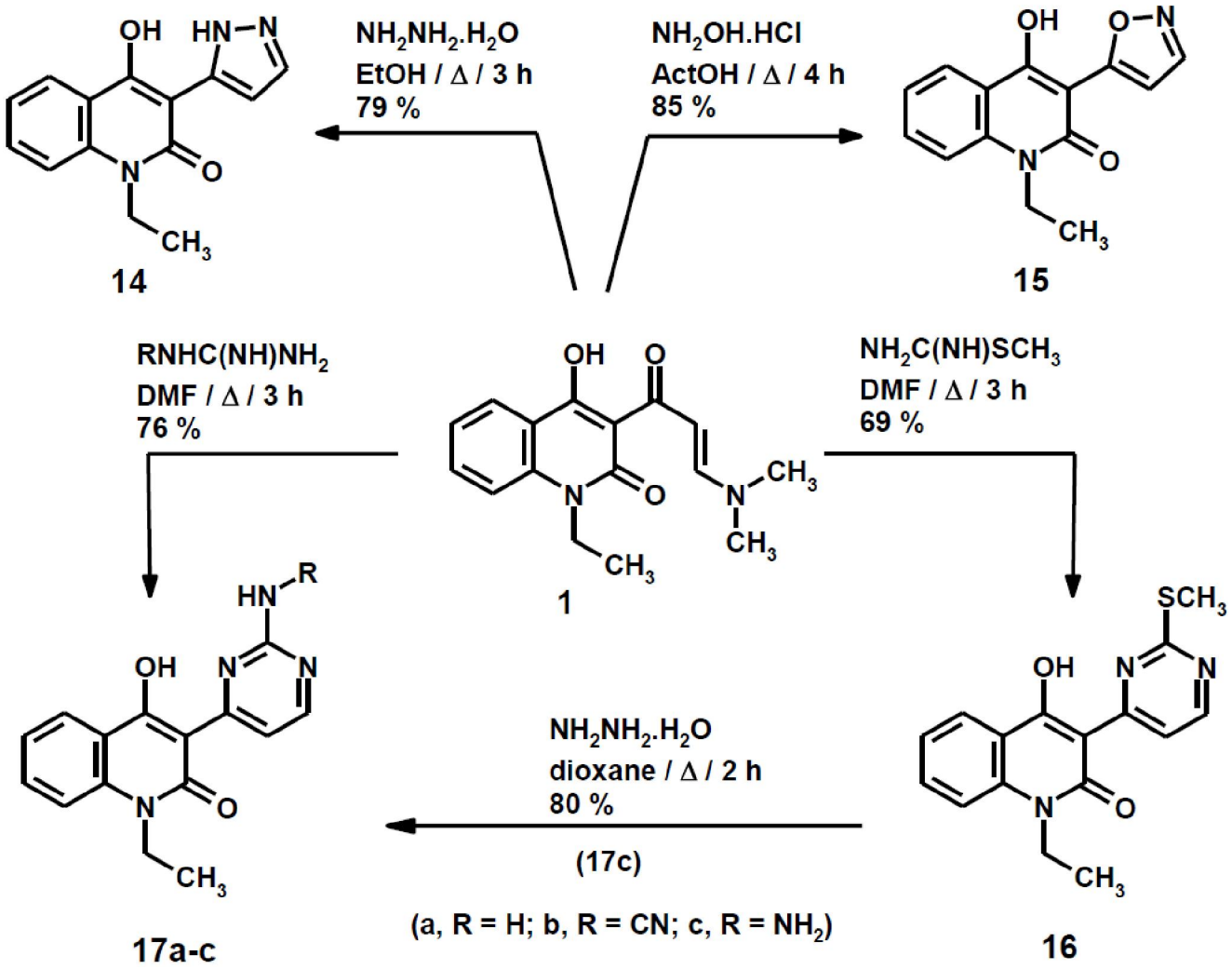
Scheme 3 : Reaction of some active methylene nitriles with the enaminone (1)

The enaminone **(1)** was reacted with hydroxylamine hydrochloride, to yield a product that may be formulated as either 3-substituted isoxazole or 5-substituted isoxazole regioisomers **(15)** (Scheme 4). ^{1}H NMR spectrum showed the existence of 3'-H proton of the isoxazole appeared at δ 8.61. This let us exclude the structure of 3-substituted isoxazole, in which one expect a more downfield chemical shift of 5'-H proton of the isoxazole due to neighboring of which to a more electronegative oxygen. This finding is in agreement with similar results which have been reported by *Chimichi et al.*[14].

The reaction of the enaminone **(1)** with *S*-methylisothiourea afforded the 2-(methylthio)pyrimidine derivative **(16)** (Scheme 4). The characterization of the structure **(16)** showed that heterocyclization is directed to take place at the enaminone chain. Thus, IR spectrum confirmed the presence of a stretching band, due to phenolic OH function, appeared at ν 3444 cm^{-1} and ^{1}H NMR spectrum revealed the disappearance of signals specific for N $(CH_3)_2$, in addition to presence of two olefinic protons appeared at more down-field chemical shifts δ 8.34 and 8.68 and with coupling constant of J 8.68 Hz specific for 5-H and 6-H protons of pyrimidine ring (TABLE 1).

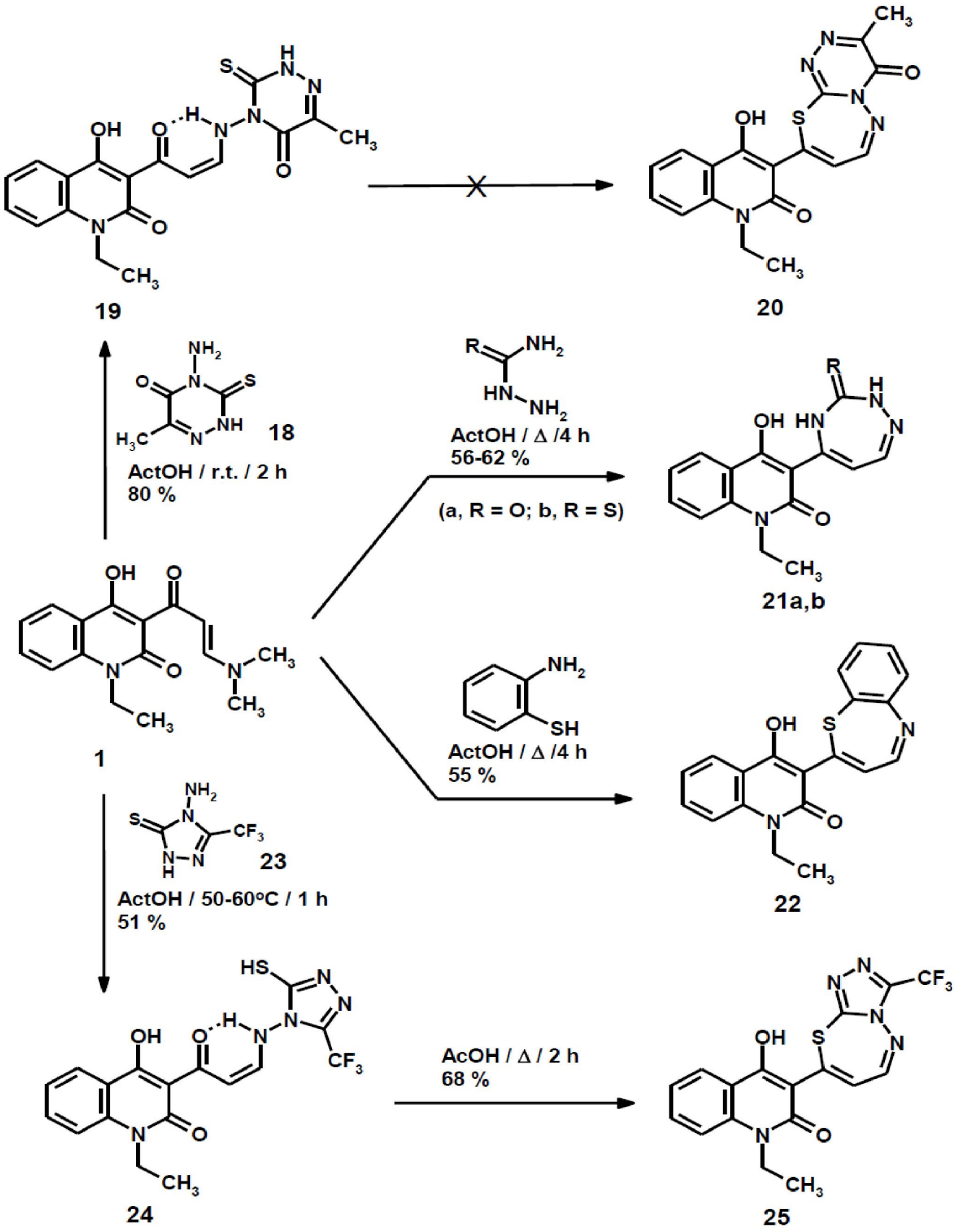
Similar treatment of the enaminone **(1)**, with guanidine hydrochloride and cyanoguanidine, furnished the corresponding 2,3-disubstituted pyrimidines **(17a)** (R = H) and **(17b)** (R = CN), respectively (Scheme 4). The analytical and spectral data of both derivatives **(17a),(17b)** were found in uniformity with the suggested

formula. ^{1}H NMR spectrum of the aminopyrimidine **(17a)** demonstrated two doublet signals at δ 8.09 and 8.42 (J = 8.1 Hz) characteristic for 5-H and 6-H of pyrimidine. IR spectrum of the cyanoaminopyrimidine **(17b)** indicated an absorption band at ν 2197 cm^{-1} specific for (HN–C≡N ↔ N=C=NH). The 3-substituted 2-hydrazinopyrimidine **(17c)** is another 2,3-disubstituted pyrimidine derivative that was obtained by the reaction of the 2-(methylthio)pyrimidine **(16)** with hydrazine hydrate, in 80% yield (Scheme 4). In addition to IR spectrum which exhibited stretching bands at ν 3427, 3336, 3272 due to NH_2 and N–H groups. ^{1}H NMR spectrum revealed the absence of the signal specific for S–CH_3 protons, beside the appearance of new two broad signals at δ 4.63 and 9.01 due to NH_2 and N–H protons, respectively (TABLE 1).



Scheme 4: Reaction of some 1,2- and 1,3-binucleophiles with the enaminone (1)

The reaction of the enaminone **(1)** with 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (**18**)[15], in glacial acetic acid, furnished the β-(triazinylamino)propenone **(19)** (Scheme 5). Surprisingly, in contrary to the enaminone **(1)**, which assumes *E*-configuration, it was proved that the enaminone **(19)** assumes Z-form. This was easily evidenced by its ^{1}H NMR spectrum. Thus, ^{1}H NMR of the enaminone **(19)** showed the appearance of two doublets at δ 7.01, (CO*CH*=CH–N), and 8.65 (COCH=*CH*–N). Both doublet signals have J = 8.5 Hz, two broad singlet which is characteristic for Z-alkenes. In addition appearance of the chemical shift of the enamine N–H, at a more down-field δ 10.91, indicated the presence of strong intramolecular hydrogen bonding which only possible in *Z*-configuration. The N-H signal of *E*-form would appear at much higher field (δ = 4–8) than those of the *Z*-form (δ = 9–13)[16]. Anyhow several attempts to carry



Scheme 5 : Reaction of some 1,4-binucleopiles with the enaminone (1)

out ring-closure of the β-(triazinylamino)propenone **(19)** in order to obtain the corresponding triazinothiadiazepinone **(20)** are not success. This may back to the previously discussed *Z*-form which steric hindered intramolecular attack and/or existence of the S-atom as thioxo rather than the nucleophilically more active thiol form.

The enaminone **(1)** was subjected to react with semicarbazide hydrochloride and thiosemicarbazide, as 1,4-binucleophiles (Scheme 5). The anticipated structure of the products; 5-substituted 1,2,4-triazepin-3-one **(21a)** and 5-substituted 1,2,4-triazepine-3-thione **(21b)**, was established on basis of elemental analyses and spectral data. For instance, ^{1}H NMR spectrum of compound **(21a)** showed the characteristic chemical shifts of two protons, at δ 12.30 and 13.40, corresponding to triazepinone ring (N–H) protons, in addition to presence of 6 aromatic protons at δ 7.33–8.07; four benzo protons and two triazepine protons (TABLE 1). Treatment of the enaminone **(1)** and *o*-aminothiophenol, in glacial acetic acid, furnished the 2-substituted 1,5-benzothiazepine **(22)** (Scheme 5). IR

TABLE 1 : Analytical and spectral data of the new compounds (2–25)

No.	M. Formula (M. Wt.)	Microanalysis Calcd./Found			IR, ν (cm^{-1})	^{1}H NMR, δ	Mass M$^+$ (I %)
		C%	H%	N%			
2	$C_{14}H_{11}NO_3$ (241.25)	69.70 69.63	4.60 4.55	5.81 5.80	1670 (C=O$_{pyrone}$), 1640 (C=O$_{quinolone}$), 1110 (C–O–C)	(DMSO-d$_6$): 1.23 (t, 3H, NCH$_2$CH$_3$), 4.26 (q, 2H, NCH$_2$CH$_3$), 7.13 (t, 1H, 9-H), 7.35 (d, 1H, 7-H), 7.58 (t, 1H, 8-H), 8.01 (d, 1H, 10-H), 8.65 (d, 1H, 3-H), 9.01 (d, 1H, 2-H)	241 (36.94)
4	$C_{14}H_{11}NO_5S$ (305.31)	55.08 55.00	3.63 3.62	4.59 4.55	3420–2900 (O–H), 1667 (C=O$_{pyrone}$), 1640 (C=O$_{quinolone}$), 1372–1189 (SO$_2$)	(CDCl$_3$): 1.21 (t, 3H, NCH$_2$CH$_3$), 4.25 (q, 2H, NCH$_2$CH$_3$), 7.26–8.16 (m, 4H, H$_{arom}$), 9.20 (s, 1H, 2-H), 14.82 (s, 1H, SO$_2$–H)	305 (7.85)
5	$C_{20}H_{23}N_3O_3S$ (385.49)	62.32 62.31	6.01 5.69	10.90 10.80	3427 (O–H), 3189 (N–H), 1679 (C=O$_{enone}$), 1634 (C=O$_{quinolone}$), 1337, 1218, 1170 (NHC=S)	(CDCl$_3$): 1.35 (t, 3H, NCH$_2$CH$_3$), 3.06 (s, 3H, N(CH$_3$)$_2$), 3.22 (s, 3H, N(CH$_3$)$_2$), 4.28 (q, 2H, NCH$_2$CH$_3$), 5.25 (d, 2H, NCH$_2$-CH=CH$_2$), 5.80 (m, 1H, NCH$_2$-CH=CH$_2$), 6.40 (d, 2H, NCH$_2$-CH=CH$_2$), 7.12– 8.25 (m, 5H, =CH–N(CH$_3$)$_2$ + H$_{arom}$), 9.52 (s, 1H, N–H), 13.45 (s, 1H, O–H)	385 (2.17)
6	$C_{20}H_{16}N_4O_6$ (408.37)	58.82 58.63	3.95 3.83	13.72 13.70	3285–3100 (N–H, O–H), 1675 (C=O), 1661 (C=O), 1630 (C=O$_{quinolone}$), 1620 (C=N). 1603	(DMSO-d$_6$): 1.20 (t, 3H, NCH$_2$CH$_3$), 4.25 (q, 2H, NCH$_2$CH$_3$), 6.35 (s, 1H, C–H$_{enol}$), 7.33–8.24 (m, 8H, H$_{arom}$), 8.58 (s, 1H, O–H$_{enol}$), 13.73 (s, 1H, O–H)	408 (5.56)
7	$C_{24}H_{20}N_4O_7$ (476.45)	60.50 60.23	4.23 4.03	11.76 11.02	3450–2800 (O–H) 1744 (C=O$_{ester}$), 1705 (C=O),1675 (C=O), 1636 (C=O$_{quinolone}$)	(DMSO-d$_6$): 1.22 (t, 3H, NCH$_2$CH$_3$), 1.92 (t, 3H, OCH$_2$CH$_3$), 4.27 (q, 2H, NCH$_2$CH$_3$), 4.48 (q, 2H, OCH$_2$CH$_3$), 7.21–8.58 (m, 9H, H$_{arom}$ + 4-H$_{pyrazole}$), 13.58 (s, 1H, O–H)	476 (22.40)
8	$C_{25}H_{21}N_5O_7$ (503.48)	59.64 59.51	4.20 4.00	13.91 13.65	3425 (O–H), 3170 (N–H), 1720 (C=O$_{ester}$), 1677 (C=O), 1638 (C=O $_{quinolone}$), 1620 (C=N), 1205 (C–O–C)	(CDCl$_3$): 1.17 (t, 3H, NCH$_2$CH$_3$), 1.73 (t, 3H, OCH$_2$CH$_3$), 4.20 (q, 2H, NCH$_2$CH$_3$), 4.41 (q, 2H, OCH$_2$CH$_3$), 7.28–8.48 (m, 9H, H$_{arom}$ + 4-H$_{pyridazine}$), 9.21 (s, 1H, N–H), 13.34 (s, 1H, O–H)	503 (28.62)
10	$C_{25}H_{20}N_4O_8$ (504.46)	59.52 59.38	4.00 3.92	11.11 10.89	3428 (O–H), 1748 (C=O$_{ester}$), 1705 (C=O$_{pyridazinone}$), 1675 (C=O), 1626 (C=O$_{quinolone}$), 1610 (C=N)	(CDCl$_3$): 1.24 (t, 3H, NCH$_2$CH$_3$), 1.82 (t, 3H, OCH$_2$CH$_3$), 4.26 (q, 2H, NCH$_2$CH$_3$), 4.43 (q, 2H, OCH$_2$CH$_3$), 7.21–8.39 (m, 9H, C-H$_{arom}$+ 4-H$_{pyridazine}$), 13.46 (s, 1H, O–H)	504 (28.73)
11	$C_{19}H_{22}N_4O_4$ (370.41)	61.61 61.60	5.99 5.90	15.13 15.08	4520, 3389, 3273 (O–H, NH$_2$), 2225 (C?N), 1685 (C=O$_{amide}$), 1678 (C=O), 1644 (C=O$_{quinolone}$)	(DMSO-d$_6$): 1.21 (t, 3H, NCH$_2$CH$_3$), 3.02 (s, 3H, N(CH$_3$)$_2$), 3.22 (s, 3H, N(CH$_3$)$_2$), 4.25 (q, 2H, NCH$_2$CH$_3$), 5.51 (d, 2H, NCHCH$_2$C=O), 5.93 (d, 2H, CONH$_2$), 6.40 (d, 1H, NCHCH(CN)CO), 6.92 (m, 1H, NCHCH(CN)CO), 7.28 (t, 1H, 6-H), 7.36 (d, 1H, 8-H), 7.68 (t, 1H, 7-H), 8.14 (d, 1H, 5-H), 13.70 (s, 1H, O–H)	370 (6.13)
12	$C_{17}H_{13}N_3O_3$ (307.31)	66.44 66.39	4.26 4.21	13.67 13.65	3440, 3355, 3181(O–H, N–H), 2216 (C?N), 1660 (C=O$_{pyridone}$), 1634 (C=O$_{quinolone}$), 1606	(DMSO-d$_6$): 1.23 (t, 3H, NCH$_2$CH$_3$), 4.32 (q, 2H, NCH$_2$CH$_3$), 7.33–8.07 (m, 6H, H$_{arom}$), 13.41 (s, 1H, O–H$_{pyridinol}$), 13.93 (s, 1H, O–H$_{quinolinol}$)	307 (36.42)

No.	M. Formula (M. Wt.)	Microanalysis Calcd./Found			IR, ν (cm^{-1})	^{1}H NMR, δ	Mass M^+ (I %)
		C%	H%	N%			
13	$C_{17}H_{14}N_4O_3$ (322.33)	63.35 63.30	4.38 4.31	17.38 17.28	3441–2750 (br, N–H, O–H), 1690 (C=$O_{pyrazolone}$), 1650 (C=$O_{quinolone}$), 1631 (C=N)	(DMSO-d_6): 1.20 (t, 3H, NCH_2CH_3), 4.26 (q, 2H, NCH_2CH_3), 7.24 (t, 1H, 6-H), 7.45 (d, 1H, 8-H), 7.66 (t, 1H, 7-H), 7.99 (d, 1H, 5-H), 8.24 (d, 1H, 5'-H), 8.45 (d, 1H, 4'-H), 9.99 (s, 1H, 7'-N–H), 10.29 (s, 1H, 2'-N–H), 13.93 (s, 1H, O–H)	322 (64.11)
14	$C_{14}H_{13}N_3O_2$ (255.28)	65.87 65.67	5.13 5.11	16.46 16.45	3426–2850 (O–H, N–H), 1633 (C=$O_{quinolone}$), 1610 (C=N)	(DMSO-d_6): 1.29 (t, 3H, NCH_2CH_3), 4.33 (q, 2H, NCH_2CH_3), 7.31–8.12 (m, 6H, H_{arom}), 13.42 (s, 1H, N–H), 14.00 (s, 1H, O–H)	255 (100)
15	$C_{14}H_{12}N_2O_3$ (256.26)	65.62 65.61	4.72 4.67	10.93 10.95	3450–2800 (O–H), 1642 (C=$O_{quinolone}$), 1610 (C=N)	(DMSO-d_6):1.25 (t, 3H, NCH_2CH_3), 4.26 (q, 2H, NCH_2CH_3), 7.02 (d, 1H, 4?H), 7.28–8.24 (m, 4H, H_{arom}), 8.61 (d, 1H, 3?H), 13.56 (s, 1H, O–H).	256 (56.08)
16	$C_{16}H_{15}N_3O_2S$ (313.38)	61.32 61.31	4.82 4.71	13.41 13.39	3444 (O–H), 1635 (C=O), 1620 (C=N)	(DMSO-d_6): 1.23 (t, 3H, NCH_2CH_3), 2.64 (s, 3H, SCH_3), 4.22 (q, 2H, NCH_2CH_3), 7.25 (t, 1H, 6-H), 7.51 (d, 1H, 8-H), 7.70 (t, 1H, 7-H), 8.01 (d, 1H, 5-H), 8.34 (d, 1H, 5'-H), 8.68 (d, 1H, 6'-H), 13.81 (s, 1H, O–H)	313 (18.79)
17a	$C_{15}H_{14}N_4O_2$ (282.30)	63.82 63.53	5.00 4.77	19.85 19.61	3459, 3272, 3151 (O–H, NH_2), 1634 (C=O), 1620 (C=N)	(DMSO-d_6): 1.28 (t, 3H, NCH_2CH_3), 4.25 (q, 2H, NCH_2CH_3), 6.63 (b, 2H, NH_2), 6.69 (d, 1H, 5'-H), 7.27 (t, 1H, 6-H), 7.55 (d, 1H, 8-H), 7.79 (t, 1H, 7-H), 8.15 (d, 1H, 5-H), 8.42 (d, 1H, 6'-H), 14.18 (s, 1H, O–H)	282 (17.32)
17b	$C_{16}H_{13}N_5O_2$ (307.31)	62.53 62.36	4.26 4.11	22.79 22.63	3451 , 3340, 3228, 3170 (O–H, N–H), 2197 (C?N), 1632 (C=O), 1614 (C=N)	(DMSO-d_6): 1.22 (t, 3H, NCH_2CH_3), 4.21 (q, 2H, NCH_2CH_3), 7.15 (d, 1H, 5'-H), 7.28 (t, 1H, 6-H), 7.46 (d, 1H, 8-H), 7.91 (t, 1H, 7-H), 8.06 (d, 1H, 5-H), 8.61 (d, 1H, 6'-H), 9.01 (s, 1H, N–H), 13.85 (s, 1H, O–H)	307 (12.45)
17c	$C_{15}H_{15}N_5O_2$ (297.32)	60.60 60.39	5.09 4.83	23.55 23.41	3427, 3336, 3272 (NH_2, N–H, O–H,), 1630 (C=$O_{quinolone}$), 1616 (C=N)	(DMSO-d_6): 1.21 (t, 3H, NCH_2CH_3), 4.25 (q, 2H, NCH_2CH_3), 4.63 (br, 2H, NH_2), 7.28 (t, 1H, 6-H), 7.36 (d, 1H, 8-H), 7.68 (t, 1H, 7-H), 7.93 (d, 1H, 5-H), 8.42 (d, 1H, 6'-H), 9.01 (br, 1H, N–H), 13.93 (s, 1H, O–H)	297 (1.22)
19	$C_{18}H_{17}N_5O_4S$ (399.43)	54.13 54.12	4.29 4.22	17.53 17.48	3480–2800 (br, H–bonded, O–H, N–H), 1679 (C=O_{enone}), 1668 (C=$O_{triazinone}$), 1635 (C=$O_{quinolone}$), 1620 (C=N), 1347, 1225 (S=C–N)	($CDCl_3$): 1.24 (t, 3H, NCH_2CH_3), 2.62 (s, 3H, 6'-CH_3), 4.29 (q, 2H, NCH_2CH_3), 7.01 (d, 1H, J = 8.5 Hz, COCH=CH–N), 7.15–8.27 (m, 4H, H_{arom}), 8.65 (d, 1H, J = 8.5 Hz, COCH=CH–N), 10.91 (s, 1H, N–$H_{enamine}$), 12.09 (s, 1H, N–$H_{triazine}$), 13.58 (s, 1H, O–H)	399 (5.63)
21a	$C_{15}H_{14}N_4O_3$ (298.30)	60.40 60.36	4.73 4.65	18.78 18.82	3435, 3159 (O–H, N–H), 1668 (C=$O_{triazepinone}$), 1628 (C=$O_{quinolone}$)	(DMSO-d_6): 1.23 (t, 3H, NCH_2CH_3), 4.32 (q, 2H, NCH_2CH_3), 7.33–8.07 (m, 6H, H_{arom}), 12.30, 13.40 (br, 2H, 2 N–H), 13.96 (s, 1H, O–H)	298 (28.71)
21b	$C_{15}H_{14}N_4O_2S$ (314.37)	57.31 57.22	4.49 4.43	17.82 17.63	3393, 3197 (O–H, N–H), 1647 (C=O), 1321, 1274 (S=C–N)	(DMSO-d_6): 1.21 (t, 3H, NCH_2CH_3), 4.24 (q, 2H, NCH_2CH_3), 7.28–8.05 (m, 6H, H_{arom}), 11.00, 11.32 (br, 2H, 2 N–H), 13.46 (s, 1H, O–H)	314 (32.24)
22	$C_{20}H_{16}N_2O_2S$ (348.43)	68.95 68.37	4.63 4.81	8.04 7.96	3429 (O–H), 1632 (C=$O_{quinolone}$), 1617 (C=N)	(DMSO-d_6): 1.28 (t, 3H, NCH_2CH_3), 4.25 (q, 2H, NCH_2CH_3), 6.53 (d, 1H, 3'-H), 7.14–8.17 (m, 9H, H_{arom} + 4'-H), 13.74 (s, 1H, O–H)	348 (100)
24	$C_{17}H_{14}F_3N_5O_3S$ (425.39)	48.00 47.85	3.32 3.20	16.46 16.26	3420, 3226, 3174 (O–H, N–H), 1660 (C=O_{enone}), 1630 (C=$O_{quinolone}$), 1623 (C=N), 1357, 1255 (S=C–N)	(DMSO-d_6): 1.23 (t, 3H, NCH_2CH_3), 2.92 (s, 1H, SH), 4.19 (q, 2H, NCH_2CH_3), 6.88 (d, J = 7.1 Hz, 1H, COCH=CH–N), 7.12–7.99 (m, 4H, H_{arom}), 8.41 (d, J = 7.1 Hz, 1H, COCH=CH–N), 11.02 (s, 1H, N–H), 13.81 (s, 1H, O–H)	425 (2.03)
25	$C_{17}H_{12}F_3N_5O_2S$ (407.38)	50.12 50.12	2.97 2.88	17.19 17.25	3445 (O–H), 1628 (C=$O_{quinolone}$), 1606 (C=N)	(DMSO-d_6): 1.17 (t, 3H, NCH_2CH_3), 4.20 (q, 2H, NCH_2CH_3), 6.87–8.14 (m, 6H, H_{arom}), 13.39 (s, 1H, O–H)	407 (19.45)

spectrum of the benzothiazepine **(22)** showed an absorption band at ν 3429 cm^{-1} due to H-bonded OH (S···H–O). ^1H NMR spectrum illustrated the disappearance of the *N,N*-dimethylamino group and a relative integration of aromatic protons at δ 7.14–8.17, equivalent to ten protons; eight benzo protons and two thiazepine protons.

When the reaction of the enaminone **(1)** and 4-amino-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol **(23)**[17] was carried out, in warm (50–60 °C) glacial acetic acid, the Z-β-(1,2,4-triazol-4-yl)amino)propenone derivative **(24)** was obtained, in 51% yield (Scheme 5). IR spectrum of the product revealed the presence of N–H group at ν 3174 cm^{-1}. ^1H NMR spectrum confirmed that (NH_2) group was involved in the nucleophile attack where no indication for its specific signal, whereas a singlet signal at δ 2.92 due to S–H group was observed. In addition a broad singlet appeared at δ 11.02 due to the proton of hydrogen-bonded N–H. This enaminone **(24)** as well as the enaminone 19 assumes *Z*-configuration by means of presence of two doublets at d 6.88 and 8.41which have J = 7.1 Hz (TABLE 1).

Intramolecular cyclization of the enaminone **(24)** was achieved, *via* boiling of which in glacial acetic acid, giving the 3,8-disubstituted triazolo[3,4-*b*]thiadiazepine **(25)**, in 68% yield (Schemes 5). IR spectrum showed an absorption band at ν 3445 cm^{-1} due to O–H group which is not extended as usual (N···H–O). ^1H NMR spectrum revealed a chemical shift at a relatively higher field δ 13.39 singlet was attributed to hydrogen-bonded O–H of the type (S···H–O). Affirming the type of H-bonding is based on recalling that chemical shift of hydrogen-bonded O–H of the type (N···H–O) usually appears at δ 14.00 ±0.25.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes on a digital Stuart SMP3. IR spectra were taken on Perkin-Elmer FT-IR 1650 spectrophotometer, using samples in KBr disks. ^1H NMR spectra were recorded on Varian Gemini-200 (200 MHz) or JEOL ECA (500 MHz) NMR spectrometers, using DMSO-d_6 or C*D*Cl_3 as the solvent and TMS as internal reference. Mass spectra were determined on a Shimadzu GC-MS-QP 1000 EX or NRC-GC/MS spectrometers by direct inlet, operating at 70 eV. Elemental microanalyses were performed on a Perkin Elmer CHN-2400 Analyzer at Cairo University and Micro analytical Center.

(E)-3-(3-(Dimethylamino)acryloyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (1)

(E)-3-(3-(Dimethylamino)acryloyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one **(1)** was prepared according to the reported literature method[1].

6-Ethyl-4*H*-pyrano[3,2-*c*]quinoline-4,5(6*H*)-dione (2)

The enaminone **(1)** (2.86 g, 10 mmol), in glacial acetic acid (20 mL) was refluxed for 2 h, and then left to cool to room temperature. The solid product so formed was collected by filtration, air dried and crystallized from DMF-water (1:1) to give dark brown crystals of the pyranoquinolinedione **(2)**. Yield 1.65 g (77 %), m.p. 137 °C (decomp.).

6-Ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-sulfinic acid (4)

To a stirred solution of the enaminone **1** (2.86 g, 10 mmol), in dry benzene (25 mL), thionyl chloride (1.18 g, 10 mmol) was added portion-wise within 1 h. The reaction mixture was left under stirring overnight. The solvent was evaporated in vacuum and the resulting oil was solidified using petroleum ether. The solid was filtrated, washed with cold ethanol and crystallized from dioxane-water (3:2) to give brown crystals of the sulfinic acid **(4)**. Yield 1.98 g (65 %), m.p. 129–130 °C.

Z-*N*-allyl-3-(dimethylamino)-2-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-prop-2-enethioamide (5)

To a solution of the enaminone **(1)** (2.86 g, 10 mmol), in DMF (20 mL), allyl isothiocyanate (0.99 g, 10.5 mmol), a few drops of triethylamine were added. The mixture was refluxed for 2 h, the solid obtained after cooling was filtrated of and crystallized from benzene to give orange crystals of the thioamide **(5)**. Yield 2.78 g (72 %), m.p. 112–114 °C.

1-Ethyl-4-hydroxy-3-(*Z*-3-hydroxy-2-[*E*-(4-nitrophenyldiazo)acryloyl]quinolin-2(1*H*)-one (6)

A cold (0–5 °C) solution of 4-

nitrobenzenediazonium chloride (1.85 g, 10 mmol) was added with continuous stirring to a cold solution of the enaminone **(1)** (2.86 g, 10 mmol), in ethanol (50 mL 95%) containing sodium acetate (1.64 g, 20 mmol). The mixture was stirred at room temperature for 1 h and the solid product so formed was collected by filtration, dried and crystallized from DMF to give deep orange crystals of the diazo-enol derivative **(6)**. Yield 3.51 g (86 %), m.p. 239–241 °C.

Ethyl 3 - (1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-1-(4-nitrophenyl)-1*H*-pyrazole-5-carboxylate (7)

To a solution of the diazo-enol derivative **(6)** (2.04 g, 5 mmol), in DMF (20 mL), fine divided potassium carbonate (2.07 g, 15 mmol) was added followed by addition of ethyl chloroacetate (1.22 g, 10 mmol), then the reaction mixture was refluxed for 3h. The solid product, so formed, was isolated by filtration, washed with ether, dried and crystallized from benzene to give yellowish crystals of the pyrazole **(7)**. Yield 1.33 g (56 %), m.p. 165–167 °C.

Ethyl 6 - (1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-3-imino-2-(4-nitrophenyl)-2,3-dihydropyridazine-4-carboxylate (8)

A mixture of the diazo-enol derivative **(6)** (2.04 g, 5 mmol) and ethyl cyanoacetate (1.13 g, 10 mmol), in dioxane (30 mL) containing few drops of piperidine, was refluxed for 4h. The solid obtained after cooling was collected by filtration, air dried and crystallized from DMF to give pale yellowish crystals of the iminopyridazine derivative **(8)**. Yield 1.66 g (66 %), m.p. 193–195 °C.

Ethyl 6 - (1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-2-(4-nitrophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylate (10)

To a suspension of the diazo-enol derivative **(6)** (2.04 g, 5 mmol), in dioxane (30 mL) diethyl malonate (1.60 g, 10 mmol), and a few drops of piperidine were added. The mixture was heated under reflux for 4h left to cool to room temperature, and then poured into water. And the solid product, so formed, was collected by filtration, dried and crystallized from DMF to give pale yellow crystals of the pyridazinone derivative **(10)**. Yield 1.87 g (74 %), m.p. 170–172 °C.

2-Cyano-3-(dimethylamino)-5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxopentanamide (11)

To a solution of the enaminone **(1)** (2.86 g, 10 mmol) and 10 mmol of either malononitrile (0.66 g) or cyanoacetamide (0.84 g), in absolute ethanol (25 mL), sodium ethoxide (0.68 g, 15 mmol) was added. The reaction mixture was refluxed on a boiling water–bath for 1 h. Then the reaction mixture was left to cool to room temperature, and acidified with diluted hydrochloric acid. The solid product so formed was filtered and crystallized from DMF to give yellowish crystals of the amide derivative **(11)**. Yield 2.85 g (77 %), m.p. 202–203 °C.

6-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (12)

The amide derivative **(11)** (1.85 g, 5 mmol), in glacial acetic acid (25 mL), was heated under reflux for 2 h. The solid precipitate that obtained after cooling was filtered and crystallized from dioxane to give colorless platelets of the pyridine-3-carbonitrile **(12)**. Yield 1.12 g (73 %), m.p. 241–1243 °C.

1-Ethyl-4-hydroxy-3-(3-oxo-3,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridin-6-yl)quinolin-2(1*H*)-one (13)

To a mixture of the enaminone **(1)** (2.86 g, 10 mmol) and 10 mmol of either 5-amino-1*H*-pyrazol-3(2*H*)-one (0.99 g) or cyanoacetohydrazide (0.99 g), in glacial acetic acid (30 mL), fused sodium acetate (1.64 g, 20 mmol) was added. The reaction mixture was heated under reflux for 3 h, then left to cool at room temperature. The precipitate so obtained was filtered, washed with cold methanol and crystallized from DMF to give colorless crystals of the pyrazolopyridine **(13)**. Yield 2.77 g (86 %), m.p. 225–226 °C.

1-Ethyl-4-hydroxy-3-(1*H*-pyrazol-5-yl)quinolin-2(1*H*)-one (14)

To a solution of the enaminone **(1)** (1.42 g, 5 mmol), in ethanol (30 mL), hydrazine hydrate (0.5 g, 10 mmol) was added. The reaction mixture was refluxed for 3h, and then cooled. The solid that deposited was filtered, and then crystallized from ethanol to give colorless crystals of the pyrazole derivative **(14)**. Yield 1.01 g (79

%), m.p. 243–245 °C.

1-Ethyl-4-hydroxy-3-(isoxazol-5-yl)quinolin-2(1*H*)-one (15)

A mixture of the enaminone **(1)** (1.42 g, 5 mmol), and hydroxylamine hydrochloride (0.35 g, 5 mmol), in acetic acid (20 mL), was heated under reflux for 4 h. The reaction mixture was left to cool to room temperature and diluted with cold water (20 mL). The solid product, so formed, was collected by filtration, dried and crystallized from ethanol to give colorless crystals of the isoxazole derivative **(15)**. Yield 1.09 g (85 %), m.p. 178–180 °C.

1-Ethyl-4-hydroxy-3-(2-(methylthio)pyrimidin-4-yl)quinolin-2(1*H*)-one (16)

A mixture of the enaminone **(1)** (1.42 g, 5 mmol), and *S*-methylisothiourea (0.45 g, 5 mmol), in DMF (15 mL), was refluxed for 3 h. Afterwards, the reaction mixture was left to cool at room temperature. The obtained the solid product was collected by filtration, dried and crystallized from dioxane-water (2:1) to give yellow crystals of the methylthiopyrimidine **(16)**. Yield 1.08 g (69 %), m.p. 176–177 °C.

3-(2-Aminopyrimidin-4-yl)-1-ethyl-4-hydroxyquinolin-2(1H)-one (17a) and N-(4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)pyrimidin-2-yl)cyanamide (17b)

To a solution of the enaminone **(1)** (2.86 g, 10 mmol), in DMF (25 mL), 10 mmol of guanidine hydrochloride (0.95 g) or cyanoguanidine (0.83 g), was added. Then the reaction mixture was heated under reflux for 3 h and afterwards left to cool at room temperature. The solid crystalline product that obtained was filtered and recrystallized to give yellowish crystals of the aminopyrimidine **(17a)** (Yield 2.15 g (76 %), m.p. 173–175 °C) and cyanoaminopyrimidine **(17b)** (Yield 2.06 g (67 %), m.p. 182–184 °C), respectively.

1-Ethyl-3-(2-hydrazinopyrimidin-4-yl)-4-hydroxyquinolin-2(1*H*)-one (17c)

A mixture of the methylthiopyrimidine **(16)** (1.57 g, 5 mmol) and hydrazine hydrate (15 mmol), in dioxane (20 mL), was heated under reflux for 2 h. The precipitate so formed on hot was filtered and recrystallized from acetic acid to give yellowish green crystals of the hydrazinopyrimidine **(17c)**. Yield 1.40 g (81 %), m.p. > 300 °C.

***Z*-1-Ethyl-4-hydroxy-3-(3-(6-methyl-5-oxo-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5*H*)-ylamino)-acryloyl)quinolin-2(1*H*)-one (19)**

A mixture of the enaminone **(1)** (1.43 g, 5 mmol) and the 4-aminotriazinone **(18)**[15] (0.80 g, 5 mmol), in glacial acetic acid (20 mL), was stirred at room temperature for 2 h. The resulting precipitate which was formed during the course of reaction was collected by filtration, washed with cold methanol, and recrystallized from dioxane/ water to give yellow crystals of the enaminone **(19)**. Yield 1.59 g (80 %), m.p. 221–223 °C.

1-Ethyl-4-hydroxy-3-(3-oxo-3,4-dihydro-2*H*-1,2,4-triazepin-5-yl)quinolin-2(1*H*)-one (21a) and 1-Ethyl-4-hydroxy-3-(3-thioxo-3,4-dihydro-2*H*-1,2,4-triazepin-5-yl)quinolin-2(1*H*)-one (21b)

A mixture of the enaminone **(1)** (1.43 g, 5 mmol) and 5 mmol of semicarbazide hydrochloride (0.38 g) and/or thiosemicarbazide (0.46 g), in glacial acetic acid (20 mL), was heated under reflux for 4 h. The reaction mixture left to cool to room temperature and diluted with cold water (20 mL), and the solid product, so formed, was collected by filtration, dried and crystallized from DMF to give pale yellow crystals of the triazepinone **(21a)** (Yield 0.84 g (56 %), m.p. 281–283 °C) and yellow crystals of the triazepinethione **(21b)** (Yield 0.97 g (62 %), m.p. 267–269 °C), respectively.

3-(1,5-Benzothiazepin-2-yl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (22)

A mixture of the enaminone **(1)** (1.43 g, 5 mmol) and *o*-aminothiophenol (0.60 mL, 5.5 mmol), in glacial acetic acid (20 mL), was heated under reflux for 4 h. The reaction mixture was left to cool at room temperature and diluted with cold water (20 mL), and the solid product, so formed, was collected by filtration, dried and crystallized from DMF to give yellowish crystals of the benzothiazepine **(22)**. Yield 0.96 g (55 %), m.p. 200–202 °C.

***Z*-1-Ethyl-4-hydroxy-3-(3-(5-thioxo-3-(trifluoromethyl)-1*H*-1,2,4-triazol-4(5*H*)-ylamino)-acryloyl)quinolin-2(1*H*)-one (24)**

A mixture the enaminone **(1)** (1.43 g, 5 mmol) and

4-amino-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol (**23**)[17] (0.92 g, 5 mmol), in glacial acetic acid (25 mL) was stirred at 50-60 °C for 1 h. The precipitated crystalline material that formed during the reaction course was filtered, washed with cold ethanol, and recrystallized from DMF to give yellowish crystals of the enaminone **(24)**. Yield 1.08 g (51 %), m.p. 162–163 °C.

1-Ethyl-4-hydroxy-3-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-8-yl)-quinolin-2(1H)-one (25)

A solution of the enaminone **(24)** (0.85 g, 2 mmol), in glacial acetic acid (10 mL), was boiled under reflux for 2 h. The acetic acid solution was left to cool at room temperature. The precipitated material was filtered, washed with methanol and recrystallized from DMF to give pale yellow crystals of the triazolothiadiazepine **(25)**. Yield 0.55 g (68 %), m.p. 191–193 °C.

CONCLUSIONS

In conclusion, *E*-3-(3-(dimethylamino)acryloyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one is beneficial synthone, for obtaining versatile novel quinolinones bearing various five-, six-, and seven-membered heterocyclic substituents at position-3, *via* its reaction with different binucleophilic reagents. Treatment of this b-enaminone with glacial acetic gives pyrano[3,2-*c*]quinoline-4,5-diones instead of the 1,3,5-triacylbenzene derivative. Coupling of the β-enaminone with *p*-nitrobenezenediazonium chloride affords arylazo-enol derivative, in which hydrolysis takes place during the course of reaction. The arylazo-enol derivative is useful substrate to obtain biheterocyclic ketones, containing quinolinone, pyrazole and pyridazine derivatives.

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