A Convenient Synthesis of 2*H*-Pyran-2-ones, Fused Pyran-2-ones, and Pyridones Bearing a Thiazole Moiety

Samir Bondock,[a,b]* Abd El-Gaber Tarhoni,[a] and Ahmed A. Fadda[a]

[a]Chemistry Department, Faculty of Science, Mansoura University, ET-35516 Mansoura, Egypt
[b]Chemistry Department, Faculty of Science, King Khalid University, 9004 Abha, Saudi Arabia
*E-mail: bondock@mans.edu.eg

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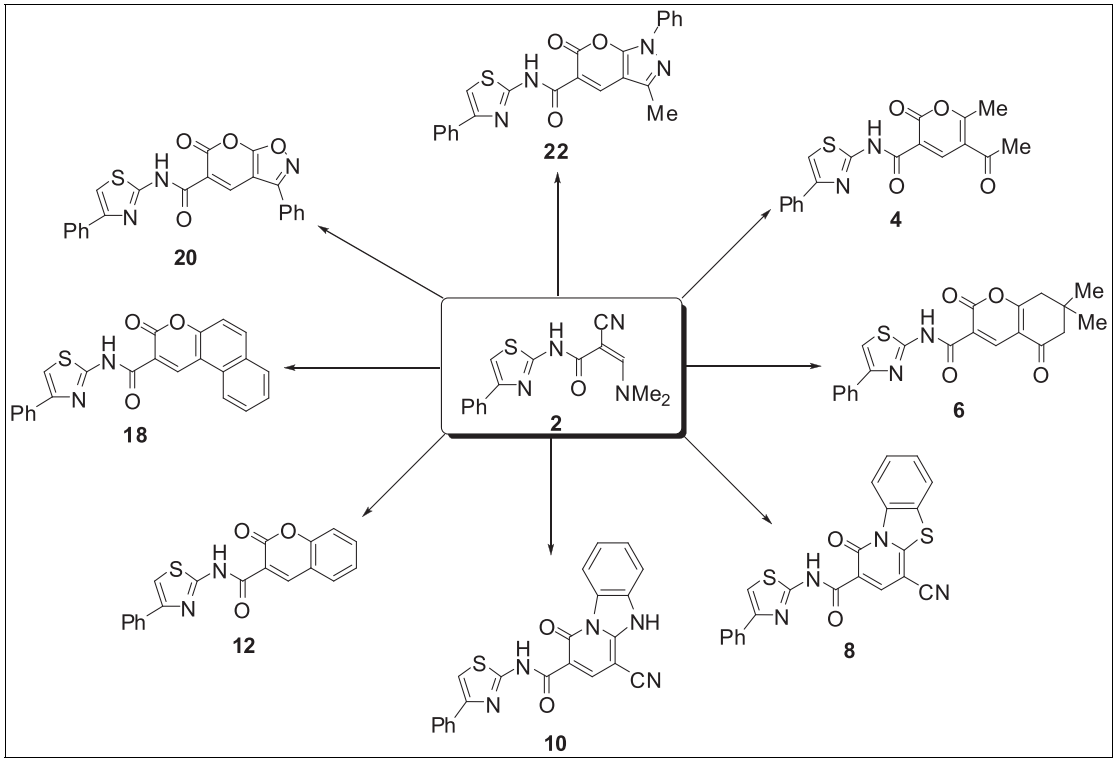

The versatile enaminonitrile, 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)-acrylamide (**2**), reacts with some *C*,*O*-binucleophiles (acetylacetone and dimedone) in refluxing acetic acid to afford the pyranone **4**, the chromene **6** derivatives, and with *C*,*N*-binucleophiles (2-(benzothiazol-2-yl)acetonitrile and 2-(1*H*-benzimidazol-2-yl)acetonitrile) to afford the respective 1*H*-pyrido[2,1-*b*]benzothiazole **8** and pyrido[1,2-*a*]benzimidazole **10** derivatives. Similar treatment of **2** with phenol, resorcinol, α-naphthol and β-naphthol in boiling acetic acid gave the coumarin derivatives **12**, **14**, **16**, and **18**, respectively. The utility of enaminonitrile **2** for the synthesis of 6*H*-pyrano[3,2-*d*]isoxazole **20**, pyrano[2,3-*c*]pyrazole **22**, and pyrano[2,3-*d*]pyrimidine **24** derivatives was also explored via its reaction with 3-phenylisoxazol-5(4*H*)-one, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one, and barbituric acid, respectively. The mechanistic aspects for the formation of the new compounds were also discussed.

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INTRODUCTION

2*H*-Pyran-2-ones and fused pyran-2-ones are important biologically active compounds [1–6]. Among fused 2*H*-pyran-2-one derivatives, 2*H*-1-benzopyran-2-one, coumarin, plays an important role in the field of synthetic and medicinal chemistry. Coumarin derivatives have exhibited various pharmacological activities as bactericides [7,8], fungicides [9], anti-inflammatory [10], anticoagulant [11], and antitumor agents [12,13]. Recently, the synthesis of various derivatives of pyran-2-one and fused pyran-2-one has attracted a great interest because many of them are nonpeptide HIV protease inhibitors [14–16].

On the other hand, the 2-pyridone moiety is found to be present in a large number of pharmaceuticals, agrochemicals, and fine chemicals [17,18]. It is also a versatile synthon that can act as a common intermediate for the synthesis of a wide variety of alkaloids [18–20]. The presence of 3-(thiazole-2-yl)carboxamido group in 2*H*-pyran-2-ones, fused 2*H*-pyranones, and pyridones opens additional possibilities for their utilization as building blocks in pharmaceutical chemistry.

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We have recently reviewed the chemistry of the synthesis and application of heterocycles derived from enaminonitriles [21] and described the behavior of 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)acrylamide towards some nitrogen nucleophiles as a possible synthetic route to attain azoles, azines, diazepine, and azoloazines [22]. In continuation of our interest in the synthesis of heterocycles containing a thiazole moiety [23–28], we report herein the results of our study of the reactions of 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)acrylamide with some *C*,*O*-binucleophiles and *C*,*N*-binucleophiles. The aim of the present paper is to present an efficient synthesis of novel 2*H*-pyran-2-ones, fused pyran-2-ones, and pyridones bearing a thiazole moiety, which have not been reported hitherto.

RESULTS AND DISCUSSION

The starting 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)acrylamide (**2**) [22] was prepared as previously described from our laboratory via condensation of 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide (**1**) [29] with dimethylformamide-dimethylacetal in refluxing toluene. Treatment of **2** with acetylacetone, as *C*,*O*-binucleophile, in glacial acetic acid under reflux, led to the formation of 5-acetyl-6-methyl-2-oxo-*N*-(4-phenylthiazol-2-yl)-2*H*-pyran-3-carboxamide (**4**). The structure of **4** was inferred from elemental analysis and spectral data. The IR spectrum revealed the disappearance of absorption band characteristic to C≡N function and the presence of absorption bands at 3238, 1719, 1672, and 1644 cm^{-1} assignable to NH, pyrone C═O, and amidic C═O functions, respectively. Its ^{1}H NMR spectrum showed three singlet signals at δ 2.12, 2.26, and 8.64 ppm specific for methyl, acetyl, and pyran (H_4) protons, respectively, and a broad singlet at δ 13.01 ppm, exchangeable with D_2O, distinctive for NH proton. The ^{13}C NMR spectrum revealed 16 carbon types; the most important signals were displayed at δ 18.9, 31.4, 162.3, 162.8, and 197.4 ppm characteristics for methyl, methyl of acetyl, pyrone carbonyl, amidic carbonyl, and ketonic carbonyl carbons, respectively. The mass spectrum showed a molecular ion peak at *m/z* = 354 (M^+) corresponding to a molecular formula $C_{18}H_{14}N_2O_4S$.

Next, we investigated the reactivity of enaminonitrile **2** towards dimedone as candidates for a facile synthetic route to attain coumarin analogues. Thus, heating **2** with dimedone in glacial acetic acid gave one isolable product that was identified as 7,7-dimethyl-2,5-dioxo-*N*-(4-phenylthiazol-2-yl)-5,6,7,8-tetrahydro-2*H*-chromene-3-carboxamide (**6**). The assignment of structure **6** was based on IR spectrum that revealed the absorption bands at 3380, 1720, 1690, and 1655 cm^{-1} assignable to NH, cyclic ester, cyclic C═O, and amidic C═O functions, respectively. The ^{1}H NMR spectrum displayed five singlet signals at δ 1.21, 1.23, 2.42, 2.68, and 8.73 ppm owing to two germinal methyl, coumarin ($2H_8$), coumarin ($2H_6$), and coumarin (H_4) protons, respectively, and a broad singlet signal at δ 12.85 ppm characteristic to the NH proton. Its mass spectrum showed a molecular ion peak at *m/z* = 394, which agrees with its molecular formula $C_{21}H_{18}N_2O_4S$.

The formation of compounds **4** and **6** was assumed to take place via the addition of the active methylene group of acetylacetone and dimedone to the activated double bond in the enaminonitrile **2** to give the nonisolable intermediates **3** and **5** those underwent *in situ* cyclization via the nucleophilic addition of the enolic hydroxyl group to the nitrile function followed by hydrolysis and loss of a dimethylamine molecule to give target compounds **4** and **6** (Scheme 1).

The reaction of enaminones with heterocyclic compounds containing active methylene group attached at α-position in respect to the ring nitrogen atom represents a simple synthetic route to achieve polyfunctionally substituted fused pyridine derivatives. With this context, we investigated the reactivity of enaminonitrile **2** towards each of 2-(benzothiazol-2-yl)acetonitrile and 2-(benzimidazol-2-yl)acetonitrile to obtain fused pyridone derivatives.

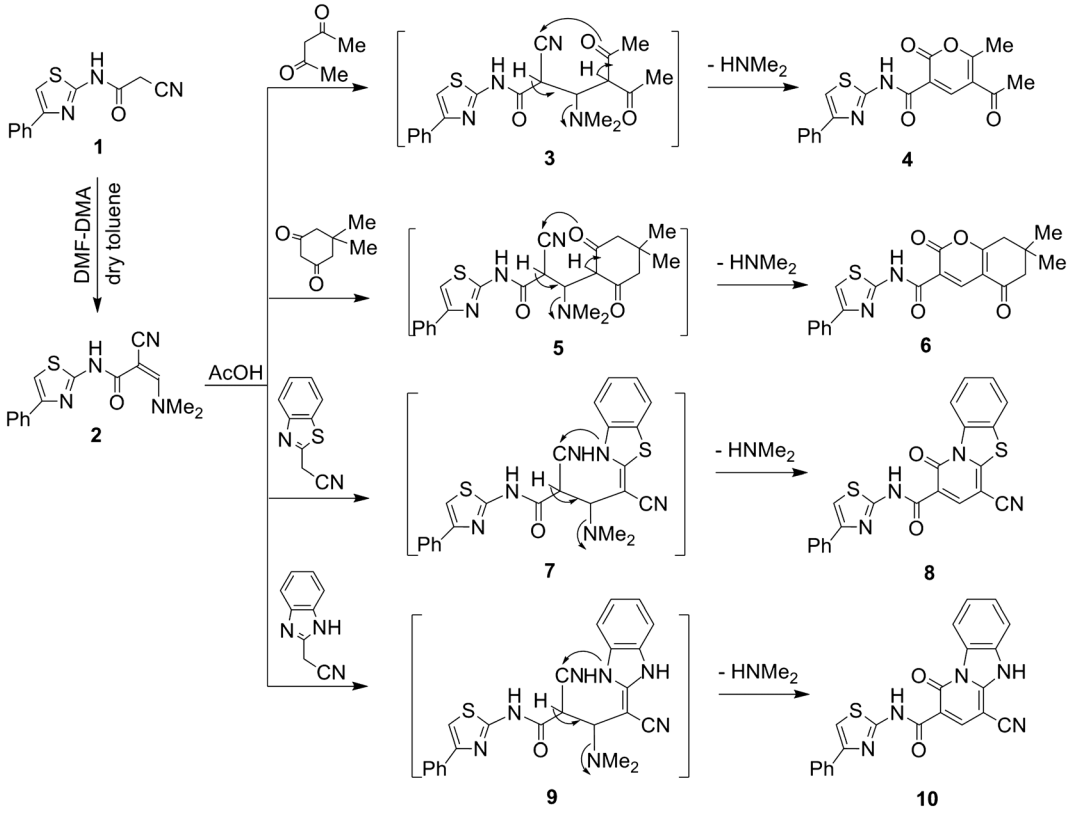
Thus, when the enaminonitrile **2** was subjected to react with 2-(benzothiazol-2-yl)acetonitrile, as *C*,*N*-binucleophile, in boiling glacial acetic acid, it afforded the *1*H-pyrido[2,1-*b*] benzothiazole derivative **8**. The structure of the latter product was confirmed on the basis of elemental analysis and spectral data. The IR spectrum exhibited absorption bands at 3360, 2219, 1695 and 1656 cm^{-1} characteristic to NH, C ≡ N, and two amidic C═O groups, respectively. Its ^{1}H NMR spectrum revealed an aromatic multiplet in the region δ 6.90–7.96 ppm, a singlet at δ 8.72 ppm due to fused pyridine (H_3) proton and a broad singlet at δ 12.71 ppm attributed to NH proton. The mass spectrum showed a molecular ion peak at *m/z* = 428 corresponding to a molecular formula $C_{22}H_{12}N_4O_2S_2$.

In a similar manner, the reaction of **2** with 2-(1*H*-benzimidazol-2-yl)acetonitrile in refluxing acetic acid afforded a single product that was identified as 4-cyano-1-oxo-*N*-(4-phenylthiazol-2-yl)-1,5-dihydropyrido[1,2-*a*] benzimidazole-2-carboxamide (**10**) based on elemental analysis and spectral data (see experimental).

The plausible mechanism for the formation of compounds **8** and **10** may be attributed to the nucleophilic addition of the active methylene group of both 2-(benzothiazol-2-yl)acetonitrile and 2-(benzimidazol-2-yl)acetonitrile to the β-carbon of the enaminonitrile **2** to give the nonisolable intermediates **7** and **9**, those underwent *in situ* intramolecular cyclization via the nucleophilic addition of the ring nitrogen atom to the nitrile function followed by hydrolysis and elimination of a dimethylamine molecule to give the target products **8** and **10**.

The forgoing results prompted us to study the reactivity of the enaminonitrile **2** towards some aromatic *C*,*O*-binucleophiles as a possible synthetic route to attain fused

Scheme 1. Reaction of enaminonitrile **2** with some *C*,*O*-binucleophiles and *C*,*N*-binucleophiles.



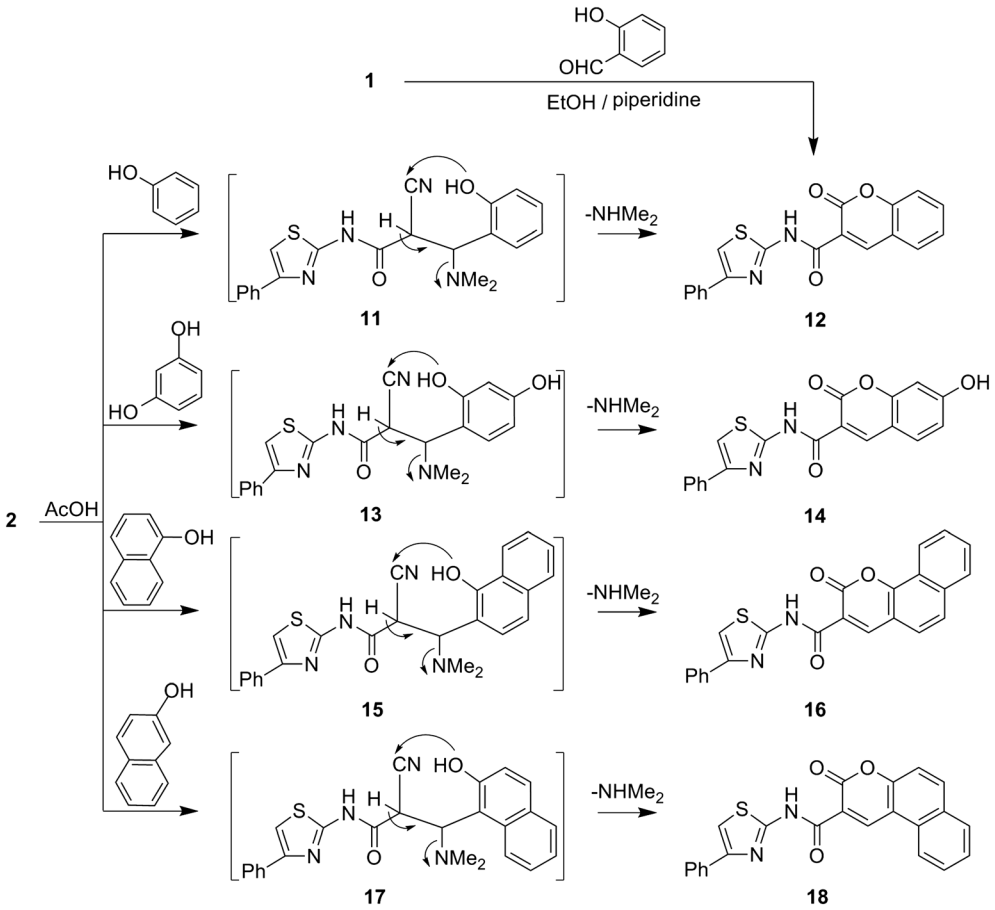
2*H*-pyran-2-ones. Phenols and their annulated naphthols are well known to be used as *C*,*O*-binucleophiles in the synthesis of condensed system of 2*H*-pyran-2-ones. In this context, we investigated the reactivity of enaminonitrile **2** to some phenols and naphthols. Thus, when **2** was subjected to react with phenol in refluxing glacial acetic acid, the reaction mixture followed up by TLC. After some time, approximately 48 h, a little pale yellow crystals got deposited, and it was identified as 2-oxo-*N*-(4-phenylthiazol-2-yl)-2*H*-chromene-3-carboxamide (**12**). The assignment of the structure of the latter product was based on its elemental analysis and spectral data (see Experimental section). Furthermore, the structure of the product **12** was confirmed by its alternative synthesis by reaction of 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide (**1**) with salicylaldehyde in refluxing ethanol containing a catalytic amount of piperidine (Scheme 2).

Similar treatment of **2** with resorcinol in glacial acetic acid under reflux afforded only one isolable product that was identified, on the basis of its spectral data and elemental analysis, as the coumarin derivative **14**. Its IR spectrum displayed the absence of C≡N stretching absorption band and the presence of absorption bands characteristic to OH, NH, cyclic ester, and amidic C═O stretching at 3450, 3365, 1719, and 1658 cm^{-1}, respectively. The ^1H NMR spectrum showed two singlets at δ 6.81 and 8.48 ppm owing to coumarin (H_8) and (H_4) protons, respectively, two doublets at δ 6.94 ($J = 5.6$ Hz) and 7.65 ppm ($J = 5.6$ Hz) due to coumarin (H_5) and (H_6) protons, and two broad singlets at δ 10.41 and 13.04 ppm owing to NH and OH protons, respectively. The mass spectrum showed a molecular ion peak at $m/z = 364$ (M^+) corresponding to a molecular formula $C_{19}H_{12}N_2O_4S$.

The reactivity of enaminonitrile **2** towards some naphthols was also examined. Thus, reaction of **2** with α-naphthol in acetic acid under reflux yielded a single product identified as 2-oxo-*N*-(4-phenylthiazol-2yl)-2*H*-benzo[*h*]chromene-3-carboxamide (**16**).

In a similar manner, treatment of **2** with β-naphthol under the same reaction condition afforded the respective 3-oxo-3*H*-benzo[*f*]chromene-2-carboxamide derivative **18**. The structure of the products **16** and **18** was elucidated on the basis of their spectra and elemental analyses. For example, the IR spectrum of **16** showed absorption bands at 3368, 1728, and 1661 cm^{-1} assignable to NH, cyclic C═O ester, and amidic C═O functions, respectively. The ^1H NMR spectrum exhibited two doublets at δ 7.77 ($J = 4.8$ Hz) and 8.50 ppm ($J = 4.8$ Hz) assignable to benzochromene (H_5) and benzochromene (H_6) protons, a multiplet signal at δ 7.29–8.02 ppm region due to aromatic protons, a singlet at δ 8.81 ppm characteristic to benzochromene (H_4) proton, and a broad singlet signal at δ 11.12 ppm assignable

Scheme 2. Reactions of enaminonitrile **2** with some phenols and naphthols.



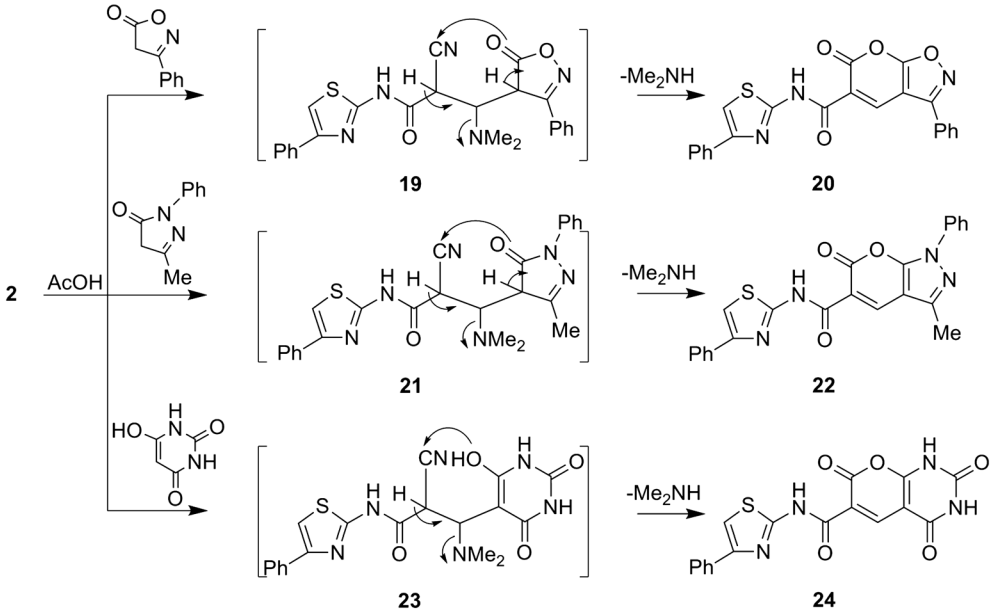
to NH proton. Its ^{13}C NMR spectrum revealed 21 carbon types; the most important signals were displayed at δ 158.4 and 164.2 ppm specific for cyclic carbonyl and acyclic carbonyl carbons. The mass spectrum showed a molecular ion peak at $m/z = 398$ (M^+) corresponding to a molecular formula $C_{23}H_{14}N_2O_3S$.

To account for the formation of the products **12**, **14**, **16**, and **18**, it is suggested as depicted in Scheme 2 that the studied reactions started with Michael-type addition of the carbon atom adjacent to hydroxyl group of each of the phenols and naphthols used to the activated double bond of **2** followed by *in situ* tandem elimination of dimethylamine and deaminative cyclization (Scheme 2).

Finally, reactions of the enaminonitrile **2** with an active methylene group incorporated into heterocyclic system, latent *C*,*O*-binucleophiles, were examined. Thus, reaction of **2** with 3-phenylisoxazol-5(4*H*)-one in refluxing glacial acetic acid afforded the corresponding 6*H*-pyrano[3,2-*d*] isoxazole derivative **20** (Scheme 3). The chemical structure of **20** was elucidated on the basis of its elemental analysis and spectral data. The IR spectrum was free of a nitrile function and showed absorption band for NH function at 3372 cm^{-1} and two sharp absorption bands at 1724 and 1671 cm^{-1} specific for pyrone C═O and amidic C═O functions, respectively. Its ^1H NMR spectrum displayed a singlet at δ 8.89 ppm due to fused pyran (H_4) proton and a broad singlet at δ 12.51 ppm, exchangeable with D_2O, specific for the NH proton. In addition, the mass spectrum showed a molecular ion peak at $m/z = 415$ (M^+) corresponding to a molecular formula $C_{22}H_{13}N_3O_4S$.

Similar treatment of **2** with 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and barbituric acid under the same reaction conditions afforded the respective pyrano[2,3-*c*] pyrazole and pyrano[2,3-*d*]pyrimidine derivatives **22** and **24**, respectively. The structures of the products **22** and **24** were elucidated on the basis of their spectra and elemental analyses. For example, the IR spectrum of compound **24** exhibited the absence of absorption band due to a nitrile function and the presence of absorption bands at 3369–3232, 1722, 1683, 1669, and 1654 cm^{-1} characteristic for three NH, pyrone C═O and three amidic C═O functions, respectively. Its ^1H NMR spectrum displayed a singlet at δ 8.61 ppm assignable to fused pyran (H_5) proton, in addition to three broad signals at δ 7.74, 9.84, and 12.76 ppm, exchangeable with D_2O, assignable to three NH protons. Its ^{13}C NMR spectrum revealed 15 carbon types, the most

Scheme 3. Reactions of enaminonitrile **2** with some heterocyclic *C*,*O*-binucleophiles.



important signals being displayed at δ 165.4, 162.9, 162.6, and 160.2 ppm specific for pyrone carbonyl, pyrimidine two carbonyl, and amidic carbonyl carbons, respectively. In addition, the mass spectrum showed a molecular ion peak at $m/z = 382$ (M^+) corresponding to a molecular formula $C_{17}H_{10}N_4O_5S$.

Here also, it is suggested that the formation of the products **20**, **22**, and **24** seems to start with Michael addition of the active methylene group of heterocycles to the activated double bond of **2** to give the nonisolable intermediates **19**, **21**, and **23**, those underwent tandem cyclization, elimination of dimethylamine, hydrolysis, and deamination to give **20**, **22**, and **24** as end products.

In conclusion, the results of the present study indicate that the enaminonitrile, *C*,*O*-binucleophile, and *C*,*N*-binucleophile are useful precursors for the facile and convenient synthesis of different functionalized 2*H*-pyran-2-one, fused 2*H*-pyran-2-ones, and pyridones bearing a thiazole moiety. In addition, they indicate that reactions of the studied enaminonitrile are regiospecific as they yielded, in each case, one product in good yield. The compounds prepared are expected to be of pharmacological interest.

EXPERIMENTAL

All melting points were determined on an electrothermal 9100 Gallenkamp apparatus (Germany). The IR spectra were measured on a Mattson 5000 FTIR spectrometer (USA) in potassium bromide disks. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker WP spectrometer (USA) (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts δ downfield from TMS as an internal standard. The mass spectra were recorded on Finnigan MAT 212 instrument (USA), and the ionizing voltage was 70 eV, at the Faculty of Science, Cairo University. Elemental analyses were carried out by the Microanalytical Unit of Faculty of Science, Cairo University, Giza, Egypt, and the results were in a good agreement (±0.3%) with the calculated values. All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merk). 2-Cyano-*N*-(4-phenylthiazol-2-yl)acetamide (**1**) [29] and 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl) acrylamide (**2**) [22] were prepared according to previously reported procedure.

General procedure for the reaction of enaminonitrile 2 with *C*,*O*-binucleophiles and *C*,*N*-binucleophiles. To a solution of enaminonitrile **2** (0.298 g, 0.001 mol) in glacial acetic acid (3–5 mL), an equimolar amount of the appropriate *C*,*O*-binucleophiles and *C*,*N*-binucleophiles was added, the mixture was heated in oil bath under reflux for 10–48 h, and then evaporated *in vacuo*. The residue was triturated with ethanol, and the resulting solid product was collected by filtration, dried well, and recrystallized from the appropriate solvent to give compounds **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, and **24**.

***5-Acetyl-6-methyl-2-oxo-N*-(4-phenylthiazol-2-yl)-2*H*-pyran-3-carboxamide (4).** This compound was prepared from acetylacetone (0.13 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

White powdered; yield 57%; mp 269–270°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3238 (NH), 1719 (pyrone C=O), 1672 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 2.12 (s, 3H, CH_3), 2.26 (s, 3H, $COCH_3$), 7.30–7.95 (m, 5H, Ar-H), 7.57 (s, 1H, thiazole H-5), 8.64 (s, 1H, pyran H-4), 13.01 (s, br, 1H, NH). ^{13}C NMR (DMSO–d_6): δ_{ppm} = 18.9 (CH_3), 31.4 (CH_3), 105.5 (thiazole C-5), 116.4 (pyran C-3), 125.6 ($2CH_{Ar}$), 127.7 (pyran C-5), 128.5 ($2CH_{Ar}$), 129.6 (CH_{Ar}), 131.4 (C_{Ar}), 153.7 (pyran C-2), 155.6 (pyran C-6), 159.9 (thiazole C-4), 162.6 (thiazole C-2), 162.8 (CONH), 163.2 (pyran C=O), 197.4 (C=O). MS *m/z* (%): 354 (M^+, 36.4), 339 (37.8), 310 (22.5), 268 (28.6), 202 (54.9), 179 (36.6), 175 (23.2), 160 (16.7), 151 (100.0), 137 (19.1), 108 (36.6), 77 (19.8), 54 (21.6).

Anal. Calcd for $C_{18}H_{14}N_2O_4S$ (354.38): C 61.01; H 3.98; N 7.90%, Found: C 61.24; H 3.83; N 7.86%.

***7,7-Dimethyl-2,5-dioxo-N*-(4-phenylthiazol-2-yl)-5,6,7,8-tetrahydro-2*H*-chromene-3-carboxamide (6).** This compound was prepared from dimedone (0.14) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Pale yellow crystal; Yield 55%; mp 279–280°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3380 (NH), 1720 (cyclic ester), 1665 (cyclic C=O), 1655 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 1.21 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.42 (s, 2H, chromene 8-CH_2), 2.68 (s, 2H, chromene 6-CH_2), 7.29–7.96 (m, 5H, Ar-H), 7.57 (s, 1H, thiazole H-5), 8.73 (s, 1H, chromene H-4), 12.85 (s, br, 1H, NH). MS *m/z* (%): 394 (M^+, 36.5), 350 (19.6), 324 (30.2), 252 (26.3), 229 (33.2), 220 (46.6), 203 (16.3), 191 (100), 175 (34.6), 160 (15.8), 123 (21.4), 77 (23.6), 58 (18.3). *Anal*. Calcd for $C_{21}H_{18}N_2O_4S$ (394.44): C 63.94; H 4.60; N 7.10%, found: C 64.04; H 4.51; N 7.02%.

***4-Cyano-1-oxo-N*-(4-phenylthiazol-2-yl)-1*H*-pyrido[2,1-*b*]benzothiazole-2-carboxamide (8)**. This compound was prepared from (benzothiazol-2-yl)acetonitrile (0.174 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Brown powdered; yield 54%; mp 281–282°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3360 (NH), 2219 (C≡N), 1695, 1656 (2 amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 6.9–7.96 (m, 9H, Ar-H), 7.49 (s, 1H, thiazole H-5), 8.72 (s, 1H, pyridobenzothiazole H-3), 12.71 (s, br, 1H, NH). MS *m/z* (%): 428 (M^+, 39.7), 376 (27.8), 320 (19.2), 253 (26.9), 225 (43.3), 203 (28.4), 175 (34.6), 160 (100), 134 (53.3), 77 (33.8), 58 (17.3). *Anal*. Calcd for $C_{22}H_{12}N_4O_2S_2$ (428.49): C 61.67; H 2.82; N 13.08%, found: C 61.48; H 2.91; N 13.22%.

***4-Cyano-1-oxo-N*-(4-phenylthiazol-2-yl)-1,5-dihydropyrido[1,2*a*]benzimidazole-2-carboxamide (10)**. This compound was prepared from (benzimidazol-2-yl)acetonitrile (0.157 g) by heating for 12 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Yellowish brown powdered; yield 56%; mp 293–294°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3410–3378 (2NH), 2215 (C≡N), 1690, 1658 (2 amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 7.05–7.96 (m, 9H, Ar-H), 7.49 (s, 1H, thiazole H-5), 8.75 (s, 1H, pyridobenzimidazole H-3), 9.18 (s, br, 1H, NH), 12.79 (s, br, 1H, NH). MS *m/z* (%): 411(M^+, 33.9), 383 (23.3), 336 (20.2), 258 (29.7), 236 (19.8), 208 (100), 203 (36.6), 175 (20.3), 160 (23.1), 133 (50.2), 77 (27.9), 54 (16.7). *Anal*. Calcd for $C_{22}H_{13}N_5O_2S$ (411.44): C 64.22; H 3.18; N 17.02%, found: C 64.04; H 3.23; N 17.14%.

***2-Oxo-N*-(4-phenylthiazol-2-yl)-2*H*-chromene-3-carboxamide (12)**. This compound was prepared from phenol (0.094 g) by heating for 48 h under reflux and recrystallized from a mixture of methanol and dimethylformamide (1:1).

Alternative method for the synthesis of compound 12. A mixture of compound **1** (0.243 g, 0.001 mol) and salicylaldehyde (0.122 g, 0.001 mol) in ethanol (30 mL) containing a little amount of piperidine (3 drops) was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and then pour onto ice cold water (25 mL) containing few drops of conc. HCl. The precipitated product was filtered off, dried well, and crystallized from a mixture of methanol and dimethylformamide (1:1) to give compound **12**.

Pale yellow crystals; yield 48%; mp 269–270°C; IR (KBr): ν_{max}/cm^{-1} = 3378 (NH), 1725 (cyclic easter), 1657 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 7.13–7.79 (m, 9H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.43 (s, 1H, chromene H-4), 10.68 (s, br, 1H, NH). MS *m/z* (%): 348 (M^+, 40.1), 304 (49.2), 271 (19.7), 203 (24.9), 175 (46.6) 173 (100), 160 (14.8), 145 (28.3), 77 (19.9), 51(28.8). *Anal*. Calcd for $C_{19}H_{12}N_2O_3S$ (348.38): C 65.51; H 3.47; N 8.04%, found: C 65.34; H 3.43; N 8.20%.

***7-Hydroxy-2-oxo-N*-(4-phenylthiazol-2-yl)-2*H*-chromene-3-carboxamide (14)**. This compound was prepared from resorcinol (0.11 g) by heating for 15 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Brown powdered; yield 62%; mp 287–288°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3450 (OH), 3365 (NH),1719 (cyclic ester), 1658 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 6.81 (s, 1H, chromene H-8), 6.94 (d, *J* = 5.6 Hz, 1H, chromene H-5), 7.65 (d, *J* = 5.6 Hz, 1H, chromene H-6), 7.28–7.77 (m, 9H, Ar-H),7.52 (s, 1H, thiazole H-5), 8.48 (s, 1H, chromene H-4), 10.41 (s, br, 1H, NH), 13.04 (s, br, 1H, OH). MS *m/z* (%): 364 (M^+, 31.8), 320 (39.7), 287 (19.7), 203 (45.3), 189 (100), 175 (18.3), 160 (26.3), 77 (28.3), 58 (20.3). *Anal.* Calcd for $C_{19}H_{12}N_2O_4S$ (364.37): C 62.63; H 3.32; N 7.69%, found: C 62.42; H 3.43; N 7.52%.

***2-Oxo-N*-(4-phenylthiazol-2-yl)-2*H*-benzo[*h*]chromene-3-carboxamide (16)**. This compound was prepared from α-naphthol (0.144 g) by heating for 16 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Deep brown powdered; yield 59%; mp 298–299°C; IR (KBr): ν_{max}/cm^{-1} = 3368 (NH), 1728 (cyclic ester), 1661 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 7.29–8.02 (m, 9H, Ar-H), 7.52 (s, 1H, thiazole H-5), 7.77 (d, *J* = 4.8 Hz, 1H, benzochromene H-5), 8.50 (d, *J* = 4.8 Hz, 1H, benzochromene H-6), 8.81 (s, 1H, benzochromene H-4), 11.12 (s, br, 1H, NH). ^{13}C NMR (DMSO–d_6): δ_{ppm} = 105.5 (thiazole C-5), 117.5 (benzopyran C-3), 119.3, 120.8, 121.6, 123.3, 125.3, 125.5, 126.2, 127.3, 127.7, 128.3, 128.8, 129.3, 131.0, 131.1, 133.6 (CH_{Ar} + C_{Ar}), 150.5 (thiazole C-4), 155.1 (thiazole C-2), 158.4 (CONH), 165.4 (benzopyran C=O). MS *m/z* (%): 398 (M^+, 24.3), 354 (33.5), 223 (100), 203 (31.3), 195 (36.6), 175 (29.9), 160 (21.3), 152 (24.8), 77 (30.4), 58 (18.6). *Anal.* Calcd for $C_{23}H_{14}N_2O_3S$ (398.43): C 69.33; H 3.54; N 7.03%, found: C 69.24; H 3.62; N 7.19%.

***3-Oxo-N*-(4-phenylthiazol-2-yl)-3*H*-benzo[*f*]chromene-2-carboxamide (18)**. This compound was prepared from β-naphthol (0.144 g) by heating for 16 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Reddish brown powdered; yield 82%; mp > 300°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3362 (NH), 1726 (cyclic ester), 1659 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 7.87–8.01 (m, 9H, Ar-H), 7.52 (s, 1H, thiazole H-5), 7.64 (d, *J* = 4.6 Hz, 1H, benzochromene H-5), 8.38 (d, *J* = 4.6 Hz, 1H, benzochromene H-6), 9.92 (s, 1H, benzochromene H-1), 11.22 (s, br, 1H, NH). *Anal*. Calcd for $C_{23}H_{14}N_2O_3S$ (398.43): C 69.33; H 3.54; N 7.03%, found: C 69.56; H 3.44; N 7.11%.

***6-Oxo-3-phenyl-N*-(4-phenylthiazol-2-yl)-6*H*-pyrano[3,2-*d*]isoxazole-5-carboxamide (20)**. This compound was prepared from 3-phenylisoxazol-5-one (0.161 g) by heating for 6 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Yellow powdered; yield 62%; mp 275–276°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3372 (NH), 1724 (cyclic ester), 1671 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 6.98–7.87 (m, 10H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.89 (s, 1H, pyranoisoxazole H-4), 12.51 (s, br, 1H, NH). MS *m/z* (%): 415 (M^+, 35.7), 371(50.6), 240 (26.6), 212 (100), 203 (54.4), 175 (36.3), 160 (17.8), 77 (18.3), 58 (22.3). *Anal*. Calcd for $C_{22}H_{13}N_3O_4S$ (415.42): C 63.61; H 3.15; N 10.12%, found: C 63.44; H 3.23; N 10.21%.

***3-Methyl-6-oxo-1-phenyl-N*-(4-phenylthiazol-2-yl)-1,6-dihydropyrano [2,3-*c*]pyrazole-5-carboxamide (22)**. This compound was prepared from 3-methyl-1-phenyl-1*H*-pyrazol-5

(4*H*)-one (0.174 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Deep yellow crystal; yield 51%; mp 284–285°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3386 (NH), 1725 (cyclic ester), 1665 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 2.21 (s, 3H, CH_3), 7.29–7.92 (m, 10H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.67 (s, 1H, pyranopyrazole H-4), 12.33 (s, br, 1H, NH). MS *m/z* (%): 428 (M^+, 43.6), 413 (29.8), 336 (22.5), 253 (100), 225 (36.4), 203 (30.2), 175 (40.6), 160 (23.7), 77 (30.3), 54 (18.3). *Anal*. Calcd for $C_{23}H_{16}N_4O_3S$ (428.46): C 64.47; H 3.76; N 13.08%, found: C 64.65; H 3.68; N 13.14%.

***2,4,7-Trioxo-N*-(4-phenylthiazol-2-yl)-2,3,4,7-tetrahydro-1*H*-pyrano[2,3-*d*]pyrmidine-6-carboxamide (24)**. This compound was prepared from barbituric acid (0.128 g) by heating for 12 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1).

Yellowish brown powdered; yield 49%; mp 122–123°C; IR (KBr): $\nu_{max.}$/cm^{-1} = 3369–3232 (3NH), 1722 (cyclic ester), 1683, 1669, 1654 (3amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 7.20–7.96 (m, 5H, Ar-H), 7.59 (s, 1H, thiazole H-5), 7.74 (s, br, 1H, NH), 8.61 (s, 1H, pyranopyrimidine H-5), 9.84 (s, br, 1H, NH), 12.76 (s, br, 1H, NH). ^{13}C NMR (DMSO–d_6): δ_{ppm} = 85.8 (C-4a), 108.6 (thiazole C-5),119.5 (C-6), 125.2 ($2CH_{Ar}$), 127.8 ($2CH_{Ar}$), 129.5 (CH_{Ar}), 131.9 (C_{Ar}), 149.3 (C-5), 155.7 (C-8a), 152.8 (thiazole C-4), 159.6 (thiazole C-2), 160.2 (CONH), 162.6 (pyrimidine C=O), 162.9 (pyrimidine C=O), 165.4 (pyran C=O). MS *m/z* (%): 382 (M^+, 27.9), 354 (36.6), 305 (23.3), 207 (100), 203 (23.3), 175 (31.6), 160 (23.7), 111 (19.5), 77 (26.3), 58 (19.9). *Anal*. Calcd for $C_{17}H_{10}N_4O_5S$ (382.35): C 53.40; H 2.64; N 14.65%, found: C 53.26; H 2.73; N 14.47%.

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