



ACCESS TO CONVENIENT SYNTHESIS OF OXAZINONE AND PYRIMIDINONE HETEROCYCLES DERIVED FROM 2(3H)-FURANONE

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The conversion of the 2(3H)-furanone into the oxazinone and pyrimidinone derivatives are studied. A 2-(furan-2-ylmethylene)-4-oxo-4-phenylbutanoyl azide **3** was synthesized to carry out these conversions through its thermolysis in dry benzene and base-catalyzed decomposition of this azide in the presence of different amines. The structures of all compounds were demonstrated from their spectral data and elemental analyses.

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Introduction

In the last decades, our research group was interested in the conversion of 2(3H)-furanones into a variety of heterocyclic systems of synthetic and biological importance. Based on their facile ring opening by nitrogen nucleophiles, these furanones were converted into acyclic products which *via* ring closure afforded many heterocycles *viz.* pyrrolones, pyridazinones, triazoles, oxadiazoles, thiazolidinones, and benzoxazinones¹⁻¹⁷. To our knowledge, the conversion of 2(3H)-furanones into pyrimidine derivatives has not been reported. Pyrimidine derivatives have a broad spectrum of biological activities. These derivatives are reported to have antiviral¹⁸, antibacterial¹⁹, anti-inflammatory²⁰, antimalarial²¹, anticancer²² and antihypertensive activities²³. In view of the previous facts, we report herein the conversion of 2(3H)-furanones into oxazinone and pyrimidinone derivatives.

Experimental section

General

Melting points were measured on Gallen Kamp electric melting point apparatus. The IR spectra were recorded using potassium bromide disks on Fourier transform infrared Thermo Electron Nicolet 7600 spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) at the Central Laboratory of Faculty of Science, Ain Shams University. The ¹H-NMR spectra were run at 400 MHz on a GEMINI 400 BB NMR spectrometer (GEMINI, Manufacturing & Engineering Inc., Anaheim, CA, USA) using tetramethyl silane (TMS) as an internal standard in deuterated dimethylsulphoxide (DMSO-*d*₆) at the Main Defence Chemical Laboratory, Cairo. The mass spectra were

recorded on Shimadzu GC-MS-QP-1000EX mass spectrometer (Shimadzu Scientific Instruments, Inc., USA) operating at 70 eV at the Microanalytical Center of Cairo University. The progress of all reactions was monitored by the thin layer chromatography using Merck Kiesel gel 60 F254 aluminum-backed plates.

General procedure for preparation of 4-(furan-2-ylmethylene)-6-phenyl-3,4-dihydro-2H-1,3-oxazin-2-one (**4**)

A solution of the azide **3** (5 mmol) in dry benzene (20 mL) was heated under reflux for one hour. The separated solid after cooling was collected by filtration and recrystallized from petroleum ether, 80-100/benzene, (2:1) to afford oxazinone **4** as red crystals; mp. 170-172°C, yield 49%. IR (KBr) (ν , cm⁻¹): 3175 (NH), 3057, 3040 (Aryl-H), 1732 (C=O_{Oxazinone}), 730, 684 (δ_{5H}). ¹H-NMR (DMSO-*d*₆): δ_H (ppm) 13.28 (s, 1H, OH, *Lactim form*, *D*₂O-Exchangeable), 13.25 (s, 1H, NH, *Lactam form*, *D*₂O-Exchangeable), 8.10-6.91 (m, 8H, Ar-H), 6.78 (s, 1H, C-H_{Oxazinone}), 6.48 (s, 1H, CH=). MS (*m/z*, %): 253 (M⁺, 46), 252 (100), 222 (62), 194 (67), 115 (34), 104 (23), 81 (36), 77 (64). Anal. Calcd. for C₁₅H₁₁NO₃ (253.07): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.08; H, 4.27; N, 5.42.

Pyrolysis of azide **3**

In 10 mL round-bottomed flask fitted with an air condenser was placed 0.5 g of the azide **3**. The flask was heated on a sand bath whereby the azide was fused. Heating was continued for another one hour. The product obtained after recrystallization from petroleum ether, 80-100/benzene, (2:1) was proved by direct comparison (mp., mixed mp. and TLC) to be the oxazinone **4**.

Reaction of the azide **3** with benzylamine

Benzylamine (2 mmol) was added dropwise to a solution of azide **3** (2 mmol) in dry benzene (20 mL) and the mixture was stirred at room temperature for 2 h or heated under

reflux for one hour. The precipitated solid was collected by filtration and recrystallized from petroleum ether, 80-100/benzene (3:1) to give benzylurea **5** and *N*-benzylpyrimidine **6**, respectively.

1-Benzyl-3-(1-(furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)urea (**5**)

Brown crystals, mp. 195-197°C, yield 52%. IR (KBr) (ν , cm^{-1}): 3247 (NH), 3059, 3028 (Aryl-H), 2937, 2922 (Alkyl-H), 1671 ($\text{C}=\text{O}_{\text{Ketone}}$), 1643 ($\text{C}=\text{O}_{\text{Amide}}$), 759, 692 (δ_{SH}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 9.51 (s, 1H, NHCO , $D_2\text{O-Exchangeable}$), 9.20 (s, 1H, NHCH_2 , $D_2\text{O-Exchangeable}$), 7.75-7.05 (m, 13H, Ar-H), 6.73, 6.56 (*Two singlets*, 1H, *E*- & *Z*-isomers, CH=), 4.33 (s, 2H, NHCH_2), 3.19-3.01 (dd, 2H, CH_2CO , $J=16.4\text{ Hz}$). MS (m/z , %): MS (m/z , %): 360 (M^+ , 10), 253 (42), 210 (50), 192 (60), 106 (3), 91 (100), 77 (51). Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$ (360.15): C, 73.32; H, 5.59; N, 7.77. Found: C, 73.21; H, 5.43; N, 7.68.

1-Benzyl-4-(furan-2-ylmethylene)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (**6**)

Yellow crystals, mp. 148-150°C, yield 47%. IR (KBr) (ν , cm^{-1}): 3259 (NH), 3065, 3021 (Aryl-H), 2955, 2935 (Alkyl-H), 1652 ($\text{C}=\text{O}$), 738, 692 (δ_{SH}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 10.04 (s, 1H, OH, *Lactim form*, $D_2\text{O-Exchangeable}$), 10.03 (s, 1H, NH, *Lactam form*, $D_2\text{O-Exchangeable}$), 7.75-7.05 (m, 13H, Ar-H), 6.83 (s, 1H, C-H_{Pyrimidine}), 6.66 (s, 1H, CH=), 4.81 (s, 2H, CH_2). MS (m/z , %): 342 (M^+ , 100), 251 (40), 223 (55), 208 (42), 166 (29), 91 (80), 77 (32). Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$ (342.14): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.21; N, 8.02.

Reaction of the azide **3** with hydrazine: Synthesis of *N*-(1-(furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)hydrazine-carboxamide (**7**)

Hydrazine (2 mmol) was added dropwise to a solution of azide **3** (2 mmol) in dry benzene (20 mL) and the mixture was stirred at room temperature. The obtained solid was collected by filtration and recrystallized from benzene to give the semicarbazide derivative **7** as brown crystals, mp. 205-207°C, yield 39%. IR (KBr) (ν , cm^{-1}): 3331, 3208 (NH, NH_2), 3064, 3032 (Aryl-H), 2923, 2859 (Alkyl-H), 1700 ($\text{C}=\text{O}_{\text{Ketone}}$), 1659 ($\text{C}=\text{O}_{\text{Amide}}$), 743, 699 (δ_{SH}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 9.01 (s, 1H, NH, $D_2\text{O-Exchangeable}$), 7.34 (s, 1H, NHNH_2 , $D_2\text{O-Exchangeable}$), 7.75-6.72 (m, 8H, Ar-H), 6.56, 6.45 (*Two singlets*, 1H, *E*- & *Z*-isomers, CH=), 4.50 (s, 2H, NH_2), 3.19-3.00 (dd, 2H, CH_2 , $J=16.4\text{ Hz}$). MS (m/z , %): 285 (M^+ , 14), 255 (39), 227 (21), 150 (12), 180 (10), 119 (20), 77 (100). Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$ (285.11): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.04; H, 5.19; N, 14.61.

Synthesis of 1-amino-4-(furan-2-ylmethylene)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (**8**)

A solution of the azide **3** (2 mmol) and hydrazine (2 mmol) in dry benzene (20 mL) was heated at 90°C for one hour. The reaction mixture was concentrated and then cooled. The obtained solid was collected by filtration and recrystallized from petroleum ether, 60-80/benzene (2:1) to

give 1-aminopyrimidinone derivative **8** as faint brown crystals, mp. 160-162°C, yield 35%. IR (KBr) (ν , cm^{-1}): 3330, 3204 (NH, NH_2), 3063, 3032 (Aryl-H), 2959, 2939 (Alkyl-H), 1659 ($\text{C}=\text{O}$), 743, 699 (δ_{SH}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 13.10 (s, 1H, NH, $D_2\text{O-Exchangeable}$), 7.94-6.81 (m, 8H, Ar-H), 6.69 (s, 1H, $\text{CH}_{\text{Pyrimidine}}$), 6.39 (s, 1H, CH=), 4.99 (s, 2H, NH_2). MS (m/z , %): 267 (M^+ , 100), 239 (21), 162 (28), 102 (19), 81 (15), 77 (30). Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$ (267.10): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.28; H, 4.75; N, 15.58.

Reaction of the azide **3** with *p*-toluidine; Synthesis of 1-(1-(furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)-3-*p*-tolylurea (**9**)

p-Toluidine (2 mmol) was added to a solution of the azide **3** (2 mmol) in dry benzene (20 mL) and the mixture was heated on water bath for 2 h. The obtained solid was collected by filtration and recrystallized from petroleum ether, 80-100/benzene (2:1) to give *p*-tolylurea derivative **9** as brown crystals, mp. 220-222°C, yield 49%. IR (KBr) (ν , cm^{-1}): 3316, 3209 (2 NH), 3088, 3025 (Aryl-H), 2915, 2858 (Alkyl-H), 1699 ($\text{C}=\text{O}_{\text{Ketone}}$), 1650 ($\text{C}=\text{O}_{\text{Amide}}$), 733, 687 (δ_{SH}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 9.80 (s, 1H, NHTolyl , $D_2\text{O-Exchangeable}$), 9.05 (s, 1H, NH, $D_2\text{O-Exchangeable}$), 7.75-6.83 (m, 8H, Ar-H), 7.19-7.17 (d, 2H, HTolyl , $J=8\text{ Hz}$), 7.05-7.03 (d, 2H, HTolyl , $J=8\text{ Hz}$), 6.73, 6.56 (*Two singlets*, 1H, *E*- & *Z*-isomers, CH=), 3.20-3.05 (dd, 2H, CH_2 , $J=16\text{ Hz}$), 2.27 (s, 3H, CH_3). MS (m/z , %): 360 (M^+ , 51), 345 (41), 270 (25), 193 (15), 119 (28), 91 (100), 77 (50). Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$ (360.15): C, 73.32; H, 5.59; N, 7.77. Found: C, 73.20; H, 5.42; N, 7.64.

Synthesis of 4-(furan-2-ylmethylene)-6-phenyl-1-*p*-tolyl-3,4-dihydropyrimidin-2(1H)-one (**10**)

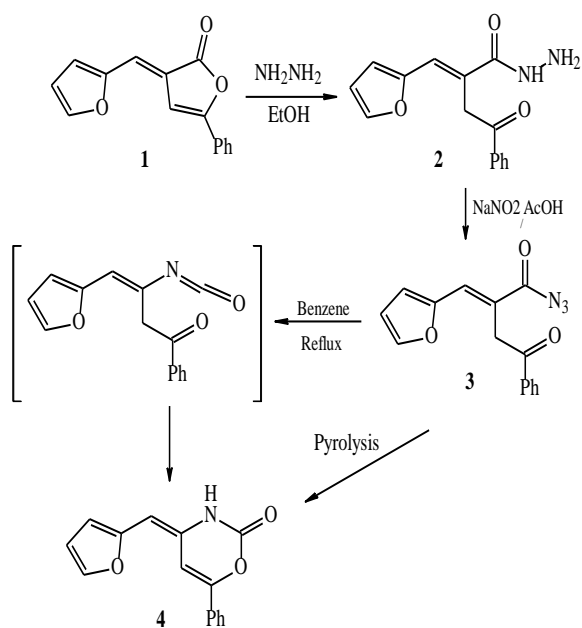
A solution of the azide **3** (2 mmol) and *p*-toluidine (2 mmol) in dry benzene (20 mL) was heated at 90°C for 6 h. The obtained solid after cooling was collected by filtration and recrystallized from benzene to give *N-p*-tolylpyrimidine derivative **10** as orange crystals, mp. 178-180°C, yield 38%. IR (KBr) (ν , cm^{-1}): 3317 (NH), 3061, 3025 (Aryl-H), 2974, 2918 (Alkyl-H), 1649 ($\text{C}=\text{O}$), 733, 687 (δ_{SH}). $^1\text{H-NMR}$ (DMSO- d_6): δ_{H} (ppm) 12.16 (s, 1H, NH, $D_2\text{O-Exchangeable}$), 7.94-7.02 (m, 8H, Ar-H), 7.27-7.25 (d, 2H, HTolyl , $J=8\text{ Hz}$), 7.08-7.06 (d, 2H, HTolyl , $J=8\text{ Hz}$), 6.68 (s, 1H, C-H_{Pyrimidine}), 6.38 (s, 1H, CH=), 2.33 (s, 3H, CH_3). MS (m/z , %): 342 (M^+ , 40), 327 (100), 252 (50), 146 (18), 102 (10), 90 (21), 77 (100). Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$ (342.14): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.05; H, 5.18; N, 8.04.

Results and discussion

Conventionally, 2-(furan-2-ylmethylene)-4-oxo-4-phenylbutanoyl azide **3** was previously prepared *via* the following two steps:

(i) The 2(3H)-furanone **1** reacted with hydrazine hydrate at room temperature in ethanol to give the acid hydrazide **2**.

(ii) The hydrazide was converted into the corresponding acyl azide **3** by the action of sodium nitrite in AcOH^7 (Scheme 1).



Scheme 1. Synthesis of compound 4.

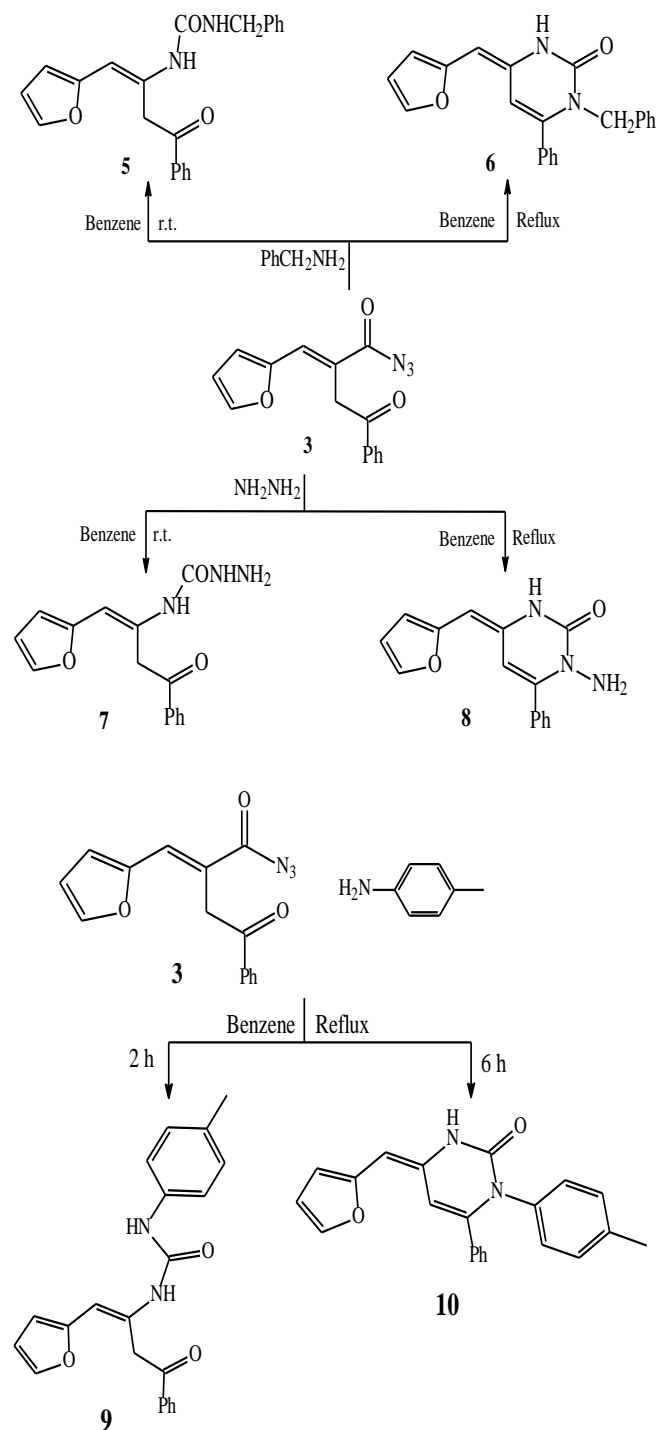
The structure of **3** was inferred from its IR spectrum which displayed ν N₃ of azide at 2142 cm⁻¹ and devoid from NH & NH₂ absorption bands.

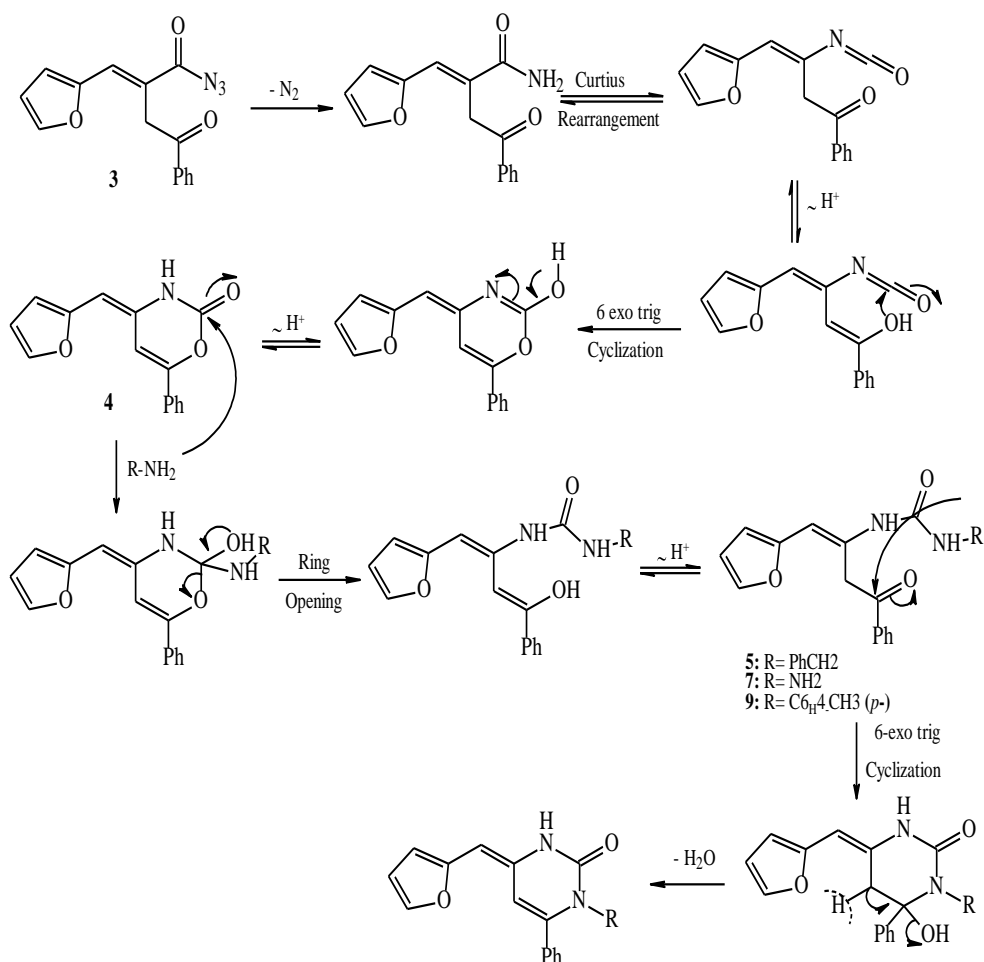
Acyl azides are known to be suitable candidates for the synthesis of many acyclic and heterocyclic derivatives *via* their acid or base-catalyzed decompositions. Thus, it was of interest to the authors to construct oxazinone and pyrimidinone derivatives using the azide **3** as a key starting material. The reactions of **3** with benzylamine, hydrazine, and *p*-toluidine were studied (Scheme 2).

Thermolysis of the azide in dry benzene led to the construction of oxazinone derivative **4** as sole product (Scheme 1). The formation of **4** can be postulated *via* loss of nitrogen gas then Curtius rearrangement of the resulting nitrene to afford isocyanate intermediate (non-isolable) followed by exo-trig ring closure (Scheme 3). The structure of **4** was substantiated from its IR spectrum which lacked ν N=C=O of isocyanate group and only displayed the stretching absorption bands of oxazinone CO and NH at ν 1732 & 3175 cm⁻¹, respectively. The ¹H-NMR spectrum was a real evidence for its existence as a mixture of lactam-lactim tautomers through which two signals at δ 13.28 and 13.25 ppm displayed, both integrated to one exchangeable proton of NH-CO \rightleftharpoons N=C-OH grouping. Moreover, the mass spectrum exhibited the correct molecular ion peak at m/z 253 (46%) as well as the base peak at m/z 252 (100%) representing [M-1] cation. The same product **4** was obtained *via* pyrolysis of the azide by fusion in neat.

When azide **3** was allowed to react with benzylamine in dry benzene at room temperature, the benzylurea derivative **5** was obtained, while the reaction in refluxing benzene for 1 h resulted in the formation of pyrimidinone derivative **6**. The structures of **5** & **6** were deduced from their analytical and spectral data. The IR spectrum of **5** revealed a broad

band at 3247 cm⁻¹ attributable to NH groups, as well as, the characteristic absorption bands for C=O of ketone and amide groups at 1671 & 1643 cm⁻¹, respectively. The ¹H-NMR spectrum of **5** showed that CH₂CO protons were magnetically non-equivalent which may be attributed to hydrogen bonding between PhC=O and NH (Cf. Experimental). The ¹H-NMR spectrum of **6** was devoid from the splitting pattern of CH₂CO group and showed a singlet band at δ 4.8 ppm due to benzyl-CH₂ protons, as well as, two signals at δ 10.03 and 10.04 ppm, both integrated to one exchangeable proton of NH-CO \rightleftharpoons N=C-OH grouping.

Scheme 2. Reactions of azide **3**



Scheme 3. Formation of the oxazinone and pyrimidinone derivatives.

The reaction of **3** with hydrazine was also dependent on the reaction conditions. Thus, stirring **3** with hydrazine in benzene at room temperature afforded the semicarbazide derivative **7** while at refluxing conditions; 1-aminopyrimidinone derivative **8** was produced. The IR spectrum of **7** showed a broad band at 3331 & 3208 cm^{-1} attributable to NH & NH₂ groups, as well as, the characteristic absorption bands for C=O of ketone and hydrazide groups at 1700 & 1659 cm^{-1} . The ¹H-NMR spectrum of **7** exhibited geminal coupling of two magnetically non-equivalent protons of CH₂ ($J=16.4$ Hz) as evidence for the aforementioned hydrogen bonding (Cf. Experimental).

The aromatic amine, *p*-toluidine, failed to affect decomposition of the azide **3** at room temperature, a behavior that may be attributed to the weak nucleophilicity of the *p*-toluidine nitrogen atom. But, when the reaction was carried out in dry benzene at 90°C for 2 h, Base-catalyzed decomposition occurred with the formation of the *p*-tolylurea derivatives **9**. On the other hand, Carrying out the reaction under reflux conditions for 6 h led to the construction of *p*-tolylpyrimidinone derivatives **10**. The IR spectrum of **9** provided the characteristic absorption bands for two NH & two C=O of ketone and amide groups at 3317 & 3209 cm^{-1} and 1699 & 1650 cm^{-1} . Also, the geminal coupling between CH₂ protons ($J=16.0$ Hz) was clearly

shown in its ¹H-NMR spectrum indicating to hydrogen bonding (Cf. Experimental). The formation of the oxazinone and pyrimidinone derivatives may be represented by

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