

A Facile One-Pot Regioselective Synthesis of [1,2,4]Triazolo[4,3-*a*]5(1*H*)-pyrimidinones via Tandem Japp–Klingemann, Smiles Rearrangement, and Cyclization Reactions

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ABSTRACT: *Coupling of active [(4-oxo-6-phenyl-3*H*-pyrimidin-2-yl)thio]methine compounds (**3**) with diazotized anilines in the presence of base gave [1,2,4]triazolo[4,3-*a*]pyrimidines (**7**). The latter products were also obtained by reactions of hydrazonoyl chlorides (**10**) with either 6-phenyl-2-thiouracil (**1**) or the 2-methylthio derivative **9**. The mechanisms and the regiochemistry of the reactions studied are discussed. © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:136–140, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10008*

INTRODUCTION

Tandem pericyclic reactions have attracted considerable attention within the past decade because of their utility in organic synthesis [1]. Other reactions in tandem have received little, if any, attention. We wish to disclose herein our finding that coupling of active [(4-oxo-6-phenyl-3*H*-pyrimidin-2-yl)thio]methine compounds (**3**) with diazotized anilines afforded directly the respective 1*H*-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones via three in situ tandem reactions, namely, Japp–Klingemann, Smiles

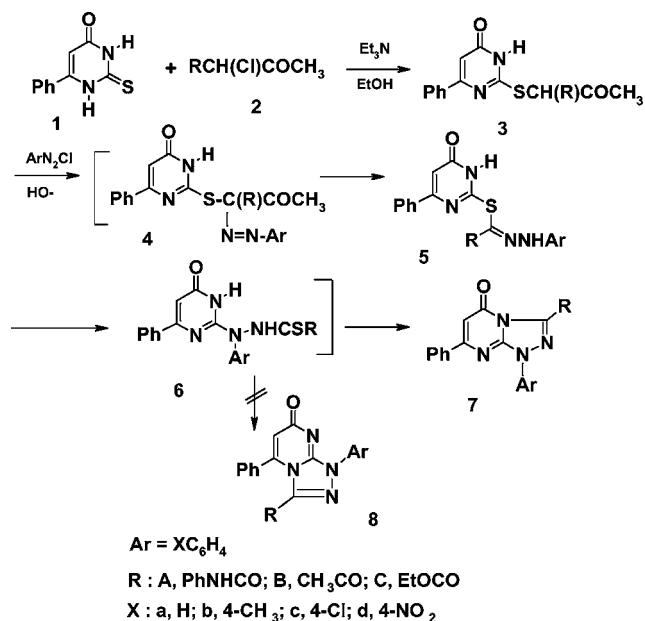
rearrangement, and cyclization reactions. Such a sequence of reactions provides a facile one-pot regioselective synthesis of the title compounds. The latter compounds are of interest as many derivatives of [1,2,4]triazolo[4,3-*a*]pyrimidine (**7**) have been reported to be useful as calcium-channel blocking vasodilators and they have antihypertensive [2], cardiovascular [3,4], anxiolytic [5] activities, as well as being components in photographic materials [6].

RESULTS AND DISCUSSION

Reaction of 6-phenyl-2-thiouracil (**1**), prepared as previously described [7], with the active chloromethylene compounds **2A–C** in ethanol in the presence of triethylamine at room temperature yielded the S-alkylated derivatives **3A–C**, respectively (Scheme 1). The structure of the latter products were evidenced by their mass, IR, and ¹H NMR spectra (see Experimental). For example, their ¹H NMR spectra showed a singlet signal at δ-2.4 assignable to the methine hydrogen. The formation of **3A–C** from **1** and **2A–C** respectively is analogous to S-alkylation reactions exhibited by 2-thiouracil derivatives [8].

Next, reaction of **3** with diazotized anilines was investigated in ethanol in the presence of sodium acetate at low temperature (0–5°C). Based on the previous literature on the Japp–Klingemann reaction [9], we anticipated that the products of this coupling reaction would be the thiohydrazonate esters (**5**) or

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SCHEME 1

their Smiles rearrangement [10] products, namely, the thiohydrazides (6). However, the mass spectral and elemental analysis data of the isolated products revealed that they were free of sulfur and thus the three structures 4–6 were discarded from further considerations (Scheme 1). The spectral and analytical data were unexpectedly consistent with either of the two isomeric [1,2,4]triazolopyrimidines 7 or 8 (Scheme 1). Distinction between these two structures was made on the basis of the ¹³C NMR and IR spectra. Literature reports [11] have shown that the chemical shift for the carbonyl carbon in 4-pyrimidinone derivatives is markedly affected by the nature of the adjacent nitrogen (pyridine type in our structure 8 and pyrrole type in our structure 7). In Chart 1, the reported chemical shift values of the annelated 4-pyrimidinones **I** and **II** are compared with the values found for the isolated products. Since the values found for the isolated products are similar to those of **I**, the regioisomeric structure **8** was im-

mediately ruled out and the isolated products were assigned structure **7**. The assignment of the latter structure **7** is further evidenced by the similarity of their carbonyl stretching frequencies (ν (C=O) = 1690–1700 cm⁻¹) with those of pyrimidinones of type **I**. For example, pyrimidinone derivatives of type **I** exhibit their CO bands in the region 1680–1690 cm⁻¹ whereas the IR spectra of type **II** show their CO bands in the region 1640–1660 cm⁻¹ [11].

To account for the direct formation of the latter products **7**, the mechanism outlined in Scheme 1 is proposed. According to this mechanism, the reaction starts with the formation of azo coupling products **4**, which undergo Japp–Klingemann elimination of the acetyl group to form the thiohydrazones **5** [12]. The latter then undergo Smiles rearrangement to yield the thiohydrazides **6** [10], which in turn undergo in situ cyclization to give **7** as the end products (Scheme 1). In all cases examined, attempts to isolate the intermediates 4–6 failed, however. This finding indicates that such intermediates are consumed as soon as they are formed under the reaction conditions employed.

To substantiate further the assigned structure **7** for the isolated products and to provide an indirect evidence for the involvement of the intermediates 4–6 and in turn the proposed mechanism, we examined alternate syntheses of the products **7** (Scheme 2). In our hands, reactions of **1** with the hydrazonoyl halides **9A–D** in ethanol in the presence of sodium ethoxide afforded products identical in all respects (m.p., mixed m.p., and IR spectra) with those obtained above. As it is well known that hydrazonoyl halides react with thiols to give the respective thiohydrazone esters [12], which undergo base-catalyzed Smiles rearrangement [10] to give the respective thiohydrazides, it is not unreasonable to assume that both reactions, namely, (**3** + ArN₂⁺ → **7**) and (**1** + **9** → **7**) proceed via the same intermediates, namely, 4–6 (Scheme 1).

The regioselective cyclization of the thiohydrazides **6** and, in turn, the assignment of structure **7** were further substantiated by alternate syntheses of **7** by reaction of 2-methylthiouracil (**10**) with hydrazonoyl halides (**9**). Thus, treatment of **10** with **9**, in ethanol, in the presence of sodium ethoxide, under reflux, was found to give products proved to be identical in all respects with products **7** obtained above. As both alkylation and acylation of 2-alkylthiouracil usually occur at N3 rather than N1 [13], it is not unreasonable to assume that reaction of **10** with **9** proceeds via the formation of the amidrazones **11**, which, in turn, undergo cyclization with elimination of methanethiol to give **7** as end products (Scheme 2).

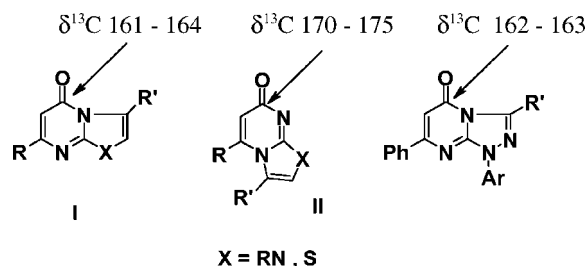
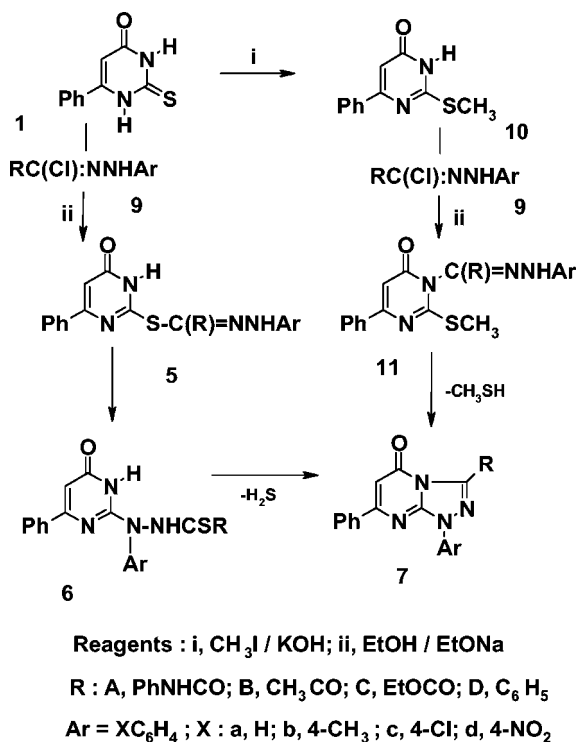


CHART 1



SCHEME 2

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using Fourier Transform Infrared and Pye Unicam SP300 Infrared spectrophotometers. ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform using a Varian Gemini 200 NMR spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX Varian MAT 711 and SSQ 7000 spectrometers. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt.

2,3-Dihydro-2-thioxo-6-phenylpyrimidin-4(1H)-one (**1**) [7], the hydrazonoyl chlorides **9A–D** [14], 2-methylthio-6-phenyl-3,4-dihydropyrimidin-4-one (**10**) [15], and the active chloromethylene compounds **2A–C** [16] were prepared as previously described.

Syntheses of Active Methine Compounds **3A** and **3B**

General method: To a mixture of equimolar quantities of pyrimidinethione **1** and the appropriate chloromethylene compound **2** (10 mmol each) in absolute ethanol (60 ml) was added triethylamine (1.4 ml, 10 mmol). The mixture was stirred at room

temperature for 24 h, then the solvent was distilled under reduced pressure and the residue was cooled. The solid that formed was collected and crystallized from dioxane–water mixture to give the respective product **3**.

Repetition of this procedure using sodium ethoxide in lieu of triethylamine afforded the respective **3** in almost the same yield.

3-Oxo-2-[(6-phenyl-4-oxo-pyrimidin-2-yl)thio]butananilide (3A). Yield 75%, m.p. 200–202°C. ν (cm^{-1}) 3288, 3100 (NH), 1718, 1662 (CO). MS m/z (%) 379 (M^+ , 11), 336 (7), 286 (53), 217 (28), 171 (59), 129 (20), 93 (100). ^1H NMR ($\text{DMSO}-d_6$) δ 2.3 (s, 3H), 4.45 (s, 1H), 6.05 (s, 1H), 7.9–8.3 (m, 10H), 10.3 (s, 1H), 10.5 (s, 1H). Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.6; H, 4.4; N, 11.3%.

3-[(6-Phenyl-4-oxo-pyrimidin-2-yl)thio]-2,4-pentanedione (3B). Yield, 70%, m.p. 212–214°C (Lit. m.p. 214°C [17]). ν (cm^{-1}) 1690, 1612. ^1H NMR ($\text{DMSO}-d_6$) δ 2.0 (s, 6H), 3.3 (s, 1H), 4.1 (s, 1H), 7.0–8.1 (m, 5H), 11.2 (s, 1H).

Synthesis of Ethyl 3-Oxo-2-[(6-phenyl-4-oxo-pyrimidin-2-yl)thio]butanoate (3C)

To a stirred solution of **1** (2.04 g, 10 mmol) in ethanol (40 ml) and DMF (10 ml) was added potassium hydroxide (0.56 g) previously dissolved in water (10 ml), followed by ethyl 2-chloro-3-oxobutanoate (**2C**) (1.38 ml, 10 mmol). The mixture was stirred for 24 h, then diluted with water. The solid that precipitated was filtered off, washed with water, and finally crystallized from ethanol to give **3C**, m.p. 202–204°C (Lit. m.p. 206°C [17]). ν (cm^{-1}) 3197, 1732, 1707, 1687, 1615. ^1H NMR ($\text{DMSO}-d_6$) δ 1.1 (t, 3H), 1.9 (s, 3H), 2.8 (s, 1H), 3.4 (q, 2H), 4.1 (s, 1H), 7.0–8.1 (m, 5H), 10.9 (s, 1H).

Synthesis of [1,2,4]Triazolo[4,3-a]pyrimidines (**7**)

Method A: To a solution of the appropriate **3** (10 mmol) in ethanol (40 ml) and DMF (10 ml) was added sodium acetate trihydrate (3 g), and the mixture was cooled in an ice bath to 0–5°C while being stirred. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride, prepared as usual by diazotizing aniline (10 mmol) in hydrochloric acid (6 ml, 6M) with sodium nitrite (0.7 g, 10 mmol) in water (10 ml). After all of the diazonium salt solution had been added, the reaction mixture was stirred for a further 30 min with cooling in the ice bath. The solid that precipitated was filtered off, washed with water,

air dried, and finally crystallized from the appropriate solvent to give the corresponding derivatives **7**.

Method B: To an ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 10 mmol) and absolute ethanol (30 ml), was added the thione **1** (10 mmoles) with stirring. To the resulting solution, was added the appropriate hydrazonoyl chloride (**9**) (10 mmol), and the mixture was stirred at room temperature for 24 h. During this period compound **9** dissolved and a new product precipitated. The latter was filtered off, washed with water, dried, and crystallized from an appropriate solvent to give the respective **7**. The latter products proved to be identical in all respects with those obtained by method A.

Method C: To a stirred ethanolic solution of sodium ethoxide, prepared from sodium metal (0.23 g, 10 mmol) and absolute ethanol (20 ml), was added **10** (10 mmol). After 10 min, the appropriate hydrazonoyl chloride (**9**) was added. The reaction mixture was refluxed until methanethiol ceased to evolve (24–40 h), and then it was cooled. The precipitated solid was filtered off, washed with water, and finally crystallized from the appropriate solvent to give the respective **7**. The products **7Aa**, **7Ba**, and **7Ca**, prepared by this method, proved to be identical in all respects with those obtained by methods A and B.

3-Phenylcarbamoyl-1,7-diphenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Aa). Yield 75%; m.p. 228–229°C (Dioxane/H₂O). ν (cm⁻¹) 3382, 1701, 1668. MS m/z (%) 407 (M⁺, 79), 302 (64), 287 (48), 171 (11), 145 (21), 129 (27), 104 (32), 91 (50), 77 (100). ¹H NMR (DMSO-*d*₆) δ 6.82 (s, 1H), 7.2–8.4 (m, 15H), 11.68 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 96.7, 119.4, 120.8, 124.5, 127.1, 128.6, 129.0, 129.7, 130.9, 133.6, 135.7, 137.5, 138.3, 147.3, 153.0, 156.6, 162.6, 163.3. Anal. Calcd. for C₂₄H₁₇N₅O₂: C, 70.75; H, 4.21; N, 17.19. Found: C, 70.7; H, 4.5; N, 17.1%.

3-Phenylcarbamoyl-1-(4-methylphenyl)-7-phenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Ab). Yield 80%, m.p. 238°C (EtOH). ν (cm⁻¹) 3110, 1697, 1668. MS m/z (%) 421 (M⁺, 80), 316 (100), 301 (49), 171 (m, 14H) (20), 129 (50), 104 (44%), 91 (93), 77 (93%). ¹H NMR (DMSO-*d*₆) δ 2.46 (s, 3H), 6.8 (s, 1H), 7.2–8.2 (m, 14H), 11.8 (s, 1H). Anal. Calcd. for C₂₅H₁₉N₅O₂: C, 71.30; H, 4.51; N, 16.6. Found: C, 71.7; H, 4.5; N, 16.5%.

3-Phenylcarbamoyl-1-(4-chlorophenyl)-7-phenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Ac). Yield 72%, m.p. 260°C (EtOH). ν (cm⁻¹) 3184, 1733, 1672. MS m/z (%) 441 (M⁺, 31), 337 (26), 322 (25), 171

(43), 129 (43), 104 (20), 91 (19), 77 (72). ¹H NMR (DMSO-*d*₆) δ 6.8 (s, 1H), 7.2–8.3 (m, 14H), 11.7 (s, 1H). Anal. Calcd. for C₂₄H₁₆ClN₅O₂: C, 65.24; H, 3.65; N, 15.85. Found: C, 65.3; H, 3.4; N, 15.6%.

3-Phenylcarbamoyl-1-(4-nitrophenyl)-7-phenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Ad). Yield 78%, m.p. 268°C (Dioxane/H₂O). ν (cm⁻¹) 3180, 1701, 1674. MS m/z (%) 452 (M⁺, 89), 407 (64), 347 (100), 332 (48), 171 (36), 129 (53), 104 (26), 91 (38), 77 (87). ¹H NMR (DMSO-*d*₆) δ 6.9 (s, 1H), 7.2–8.7 (m, 14H), 11.6 (s, 1H). Anal. Calcd. for C₂₄H₁₆N₆O₄: C, 63.71; H, 3.56; N, 18.58. Found: C, 63.6; H, 3.8; N, 18.4%.

3-Acetyl-1,7-diphenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Ba). Yield 67%, m.p. 170–172°C (Dioxane/H₂O). ν (cm⁻¹) 1701, 1680. MS m/z (%) 331 (M⁺, 98), 288 (24), 261 (19), 171 (18), 129 (24), 104 (13), 91 (43), 77 (100). ¹H NMR (DMSO-*d*₆) δ 2.5 (s, 3H), 6.9 (s, 1H), 7.5–8.2 (m, 10H). Anal. Calcd. for C₁₉H₁₄N₄O₂: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.0; H, 4.3; N, 16.5%.

3-Acetyl-1-(4-methylphenyl)-7-phenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Bb). Yield 64%, m.p. 200–203°C (Dioxane/H₂O). ν (cm⁻¹) 1705, 1680. MS m/z (%) 344 (M⁺, 100), 301 (43), 275 (24), 171 (22), 129 (25), 104 (36), 91 (48), 77 (54). ¹H NMR (DMSO-*d*₆) δ 2.3 (s, 3H), 2.76 (s, 3H), 6.84 (s, 1H), 7.2–8.2 (m, 9H). Anal. Calcd. for C₂₀H₁₆N₄O₂: C, 69.76; H, 4.68; N, 16.20. Found: C, 70.0; H, 4.8; N, 16.5%.

3-Acetyl-1-(4-chlorophenyl)-7-phenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Bc). Yield 80%, m.p. 148–149°C (EtOH). ν (cm⁻¹) 1700, 1682. MS m/z (%) 364 (M⁺, 100), 321 (35), 296 (31), 171 (37), 129 (47), 104 (15), 91 (36), 77 (50). ¹H NMR (DMSO-*d*₆) δ 2.76 (s, 3H), 6.86 (s, 1H), 7.2–8.3 (m, 9H). Anal. Calcd. for C₁₉H₁₃ClN₄O₂: C, 62.56; H, 3.59; N, 15.36. Found: C, 62.8; H, 3.7; N, 15.2%.

3-Acetyl-1-(4-nitrophenyl)-7-phenyl-1,2,4-triazolo[4,3-*a*]-5(1*H*)-pyrimidinone (7Bd). Yield 75%, m.p. 222°C (Dioxane/H₂O). ν (cm⁻¹) 1700, 1674. MS m/z (%) 375 (M⁺, 100), 332 (11), 328 (10), 305 (19), 171 (20), 129 (13), 103 (42), 90 (13), 77 (18). ¹H NMR (DMSO-*d*₆) δ 2.77 (s, 3H), 6.8 (s, 1H), 7.5–7.9 (m, 9H). ¹³C NMR (DMSO-*d*₆) δ 20.5, 97.0, 119.8, 121.1, 124.7, 127.3, 128.8, 129.8, 131.0, 136.0, 137.7, 153.0, 156.6, 162.8, 192.1. Anal. Calcd. for C₁₉H₁₃N₅O₄: C, 60.80; H, 3.49; N, 18.66. Found: C, 60.8; H, 3.2; N, 18.5%.

Ethyl 1,7-Diphenyl-1,2,4-triazolo[4,3-a]-5(1H)-pyrimidinone-3-carboxylate (7Ca). Yield 80%, m.p. 138°C (Dioxane/H₂O). ν (cm⁻¹) 1751, 1695. MS m/z (%) 361 (M⁺, 100), 287 (31), 233 (16), 171 (25), 129 (25), 104 (25), 91 (89), 77 (74). ¹H NMR (DMSO-*d*₆) δ 1.39 (t, 3H), 4.52 (q, 2H), 6.74 (s, 1H), 7.5–8.2 (m, 10H). Anal. Calcd. for C₂₀H₁₆N₄O₃: C, 66.66; H, 4.48; N, 15.50. Found: C, 66.5; H, 4.2; N, 15.2.

Ethyl 1-(4-Methylphenyl)-7-phenyl-1,2,4-triazolo[4,3-a]-5(1H)-pyrimidinone-3-carboxylate (7Cb). Yield 72%, m.p. 166–168°C (EtOH). ν (cm⁻¹) 1751, 1701. –MS m/z (%) 374 (M⁺, 100), 301 (37), 246 (15), 171 (14), 129 (32), 104 (46), 91 (49), 77 (67). ¹H NMR (CDCl₃) δ 1.49, (t, 3H), 2.4 (s, 3H), 4.6 (q, 2H), 6.6 (s, 1H), 7.3–8.1 (m, 9H). Anal. Calcd. for C₂₁H₁₈N₄O₃: C, 67.37; H, 4.8; N, 14.96. Found: C, 67.7; H, 4.2; N, 14.6%.

Ethyl 1-(4-Chlorophenyl)-7-phenyl-1,2,4-triazolo[4,3-a]-5(1H)-pyrimidinone-3-carboxylate (7Cc). Yield 75%, m.p. 136–138°C (EtOH). ν (cm⁻¹) 1751, 1695. MS m/z (%) 394 (M⁺, 100), 321 (21), 265 (10), 171 (12), 129 (26), 103 (21), 91 (32), 77 (26). ¹H NMR (CDCl₃) δ 1.5 (t, 3H), 4.6 (q, 2H), 6.6 (s, 1H), 7.3–8.3 (m, 9H). ¹³C NMR (CDCl₃) δ 13.2, 63.2, 97.1, 122.1, 127.0, 128.5, 129.2, 130.6, 131.6, 134.8, 135.1, 135.8, 147.4, 155.2, 156.3, 162.2. Anal. Calcd. for C₂₀H₁₅ClN₄O₃: C, 60.84; H, 3.83; N, 14.19. Found: C, 60.5; H, 3.9; N, 14.2%.

*Ethyl 1-(4-Nitrophenyl)-7-phenyl-1,2,4-triazolo[4,3-*pta*]-5(1H)-pyrimidinone-3-carboxylate (7Cd).* Yield 75%, m.p. 210–212°C (EtOH). ν (cm⁻¹) 1753, 1701. MS m/z (%) 405 (M⁺, 100), 360 (10), 332 (10), 279 (14), 171 (11), 129 (26), 105 (10), 91 (27), 77 (22). ¹H NMR (DMSO-*d*₆) δ 1.5 (t, 3H), 4.62 (q, 2H), 6.68 (s, 1H), 7.2–8.7 (m, 9H). ¹³C NMR (DMSO-*d*₆) δ 13.2, 63.3, 97.9, 120.3, 125.0, 127.3, 128.7, 131.0, 135.5, 135.7, 140.9, 145.1, 147.8, 155.2, 156.2, 162.2. Anal. Calcd. for C₂₀H₁₅N₅O₅: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.0; H, 3.5; N, 17.0%.

1,3,7-Triphenyl-1,2,4-triazolo[4,3-a]-5(1H)-pyrimidinone (7Da). Yield 72%, m.p. 180–181°C (MeOH). ν (cm⁻¹) 1700. MS m/z (%) 365 (74), 364 (80), 233 (10), 194 (5), 103 (25), 91 (100), 77 (35), 64 (36). ¹H NMR (DMSO-*d*₆) δ 6.6 (s, 1H), 7.4–8.3 (m, 15H). ¹³C NMR (DMSO-*d*₆) δ 97.1, 120.6, 126.1, 127.0, 127.1, 127.4, 128.7, 129.3, 130.3, 130.4, 130.7, 136.1, 136.5, 144.1, 148.3, 156.7, 161.4. Anal. Calcd. for C₂₃H₁₆N₄O: C, 75.81; H, 4.43; N, 15.37. Found: C, 76.0; H, 4.3; N, 15.2%.

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