Addition of C-nucleophiles to 5-phenylpyrimidin-2(1*H*)-ones and 6-phenyl-1,2,4-triazin-3(2*H*)-one

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Abstract

Addition reactions of C-nucleophiles to the C=N bond of 5-phenyl- and 1-methyl-5-phenylpyrimidin-2(1*H*)-ones **1a**,**b** and 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** were investigated. **1a**,**b** and **2** furnished addition products with indoles; **1a** also added *N*-methylpyrrole. Only **2** added thiophene and methyl ketones, and reacted with alkyl halides and acetone forming products resulting both from alkylation and from addition of acetone at positions 2 and 5, respectively.

Keywords: Pyrimidinones, 1,2,4-triazinones, indoles, nucleophilic addition reactions, aza-Friedel-Crafts reactions

Introduction

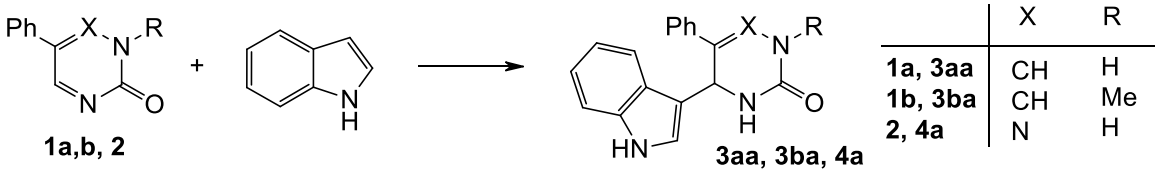
Pyrimidinones and 1,2,4-triazinones are analogs of the pyrimidine bases of nucleic acids. Therefore, they possess a big potential in the search for new biologically active compounds. They are interesting as potential agonists and antagonists of pyrimidine derivatives, widespread in nature.[1] Thus, 5-substituted pyrimidin-2-ones exhibit metaphase-arresting activity,[2] their nucleoside derivatives show anticancer[3] and antivirus activity.[4] Derivatives of 1,2,4-triazin-3(2*H*)-ones are also of interest as anticancer[5], antivirus[6] and antibacterial drugs.[7]

Pyrimidin-2-ones and 1,2,4-triazin-3(2*H*)-ones are π-deficient heterocycles susceptible to addition reactions of C-nucleophiles.[8] Pyrimidin-2-ones add organometallic compounds[9] and indoles.[10] Also known are reactions of 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** with N-nucleophiles[11] and some C- and O-nucleophiles.[12]

In this work we report on different ways for introducing C-nucleophiles into 5-phenylpyrimidin-2(1*H*)-ones **1a,b** and its 6-aza analog, 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** via direct C–C coupling (without using organometallic compounds that would require low temperatures and an inert atmosphere). Previously, it has been reported that unsubstituted, protonated pyrimidines in benzene/trifluoroacetic acid solution react with C-nucleophiles to give addition products.[13] It has been shown also that 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** reacts with various C-nucleophiles without activation, simply upon heating.[12b] These reactions constitute so-called aza-Friedel-Crafts reactions of nucleophilic hetarenes, but can be considered also as nucleophilic additions onto conjugated C=N double bonds in the presence of Lewis[14] and Bronsted[15] acids. Pyrimidin-2(1*H*)-ones and 1,2,4-triazin-3(2*H*)-ones contain such electrophilic functionalities capable of participating in aza-Friedel-Crafts reactions under similar conditions.

Results and Discussion

First, we studied the interactions of 5-phenylpyrimidin-2(1*H*)-ones **1a,b** and 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** with indole, a common nucleophile for aza-Friedel-Crafts reactions. (Scheme 1).

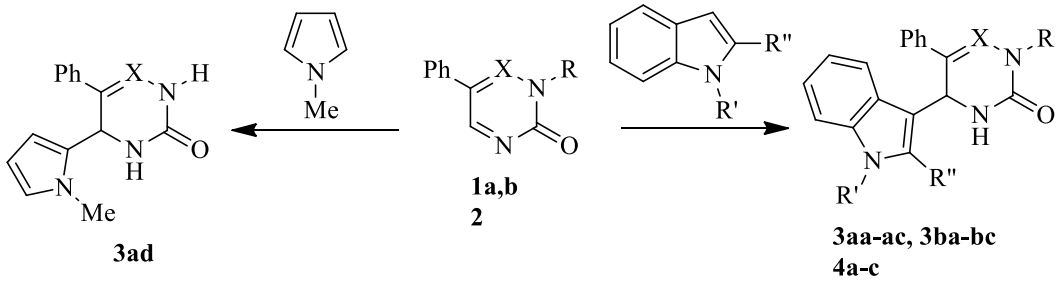


Scheme 1

The reaction of **1a** with indole in refluxing DMF as well as in a mixture of dichloromethane, ethanol and trifluoroacetic acid (or triflic acid) at room temperature gave no product. The reaction carried out in refluxing acetic acid or in chloroform/trifluoroacetic acid at room temperature afforded **3aa** in moderate yields (42% and 28%, respectively). The reaction of **2** with indole in refluxing DMF or in refluxing acetic acid gave **4a** in high yields (75% and 86%, respectively). Carrying out the reaction in chloroform/trifluoroacetic acid at room temperature afforded **4a** with lower yield (48%). Attempts to add indole to azinones **1a**,**b**, and **2** under conditions typical for Friedel-Crafts reactions, namely activation by Lewis acids such as $BF_3{\cdot}OMe_2$, $Cu(OTf)_2$, or $Co(OTf)_2$ in methanol, acetonitrile or acetic acid were unsuccessful in most cases. The reaction did not occur at room temperature, heating gave rise to tarring. The use of a Lewis acid was successful only in the reaction of **2** with indole in acetic acid and in the presence of $Co(OTf)_2$ yielding **4a** (15%). In most cases, 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** appeared to be more reactive than 5-phenylpyrimidin-2(1*H*)-one **1a**.

From the reactions of 5-phenylpyrimidin-2(1*H*)-ones **1a,b** and 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** with indoles, addition products **3aa–ac, 3ba–bc, 4a–c** were isolated (Table 1). **1a** reacted with *N*-methylpyrrole affording **3ad**, but there was no addition product isolated from the reaction of azinones **1b, 2** with pyrroles because the latter tend to polymerize in acidic solutions.

Table 1. Reaction of C-nucleophiles with **1a**,**b** and **2**; formation of addition products **3** and **4**

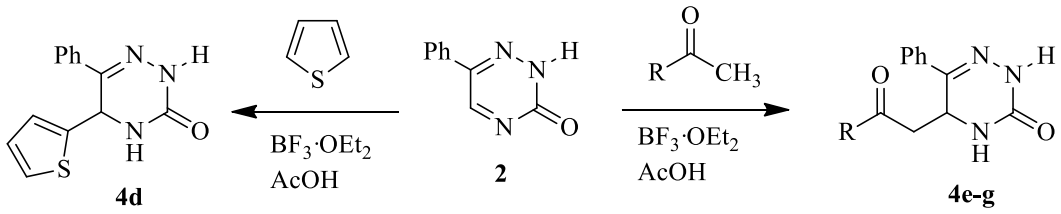


Nu	Starting material	X	R	R'	R"	Product	Yield [%]
1*H*-indol-3-yl	**1a**	CH	H	H	H	**3aa**	28
1*H*-indol-3-yl	**2**	N	H	H	H	**4a**	48
1*H*-indol-3-yl	**1b**	CH	Me	H	H	**3ba**	84
1-methyl1*H*-indol-3-yl	**1a**	CH	H	Me	H	**3ab**	42
1-methyl1*H*-indol-3-yl	**2**	N	H	Me	H	**4b**	63
1-methyl1*H*-indol-3-yl	**1b**	CH	Me	Me	H	**3bb**	73
2-methyl1*H*-indol-3-yl	**1a**	CH	H	H	Me	**3ac**	55
2-methyl1*H*-indol-3-yl	**2**	N	H	H	Me	**4c**	48
2-methyl1*H*-indol-3-yl	**1b**	CH	Me	H	Me	**3bc**	50
1-methyl-1*H*-pyrrol-2-yl	**1a**	CH	H	–	–	**3ad**	28

We also investigated the reactions of **1a**,**b** and **2** with thiophene and methyl ketones. In refluxing acetic acid or in chloroform in the presence of trifluoroacetic acid no addition products were formed, presumably due to the lower nucleophilicity of these compounds as compared to indoles. However, in refluxing acetic acid and catalyzed by $BF_3 \cdot OMe_2$, 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** afforded addition products **4d**–**4g** (Table 2).

Unlike the addition of thiophene to **2** yielding **4d**, 2-acetothienone adds to **2** with the methyl group producing **4f**; obviously, the acetyl group of 2-acetothienone lowers the nucleophilicity of the thiophene ring and the enol tautomer of the acetyl group is acting as nucleophile. Similarly, the methyl groups of acetophenone and acetone add to the C=N functionality in **2** affording products **4e** and **4g**, respectively.

Table 2. Conversion of **2** into addition products **4d**–**g**



Nu	R	Product	Yield [%]
thiophen-2-yl	–	**4d**	43
2-oxo-2-phenyethyl	Ph	**4e**	59
2-oxo-2-(thiophen-2-yl)ethyl	thiophen-2-yl	**4f**	41
2-oxopropyl	Me	**4g**	42

5-Phenylpyrimidin-2(1*H*)-ones **1a,b** did not undergo addition reactions with the reactants listed in Table 2 under the conditions applied to their reactions with **2**; also the reaction in refluxing acetone in the presence of hydrochloric acid failed.[16]

The ^{1}H and ^{13}C NMR data of **4e** did not allow an unambiguous structure proof; therefore, the structure of **4e** was confirmed by X-ray analysis (Figure 1).

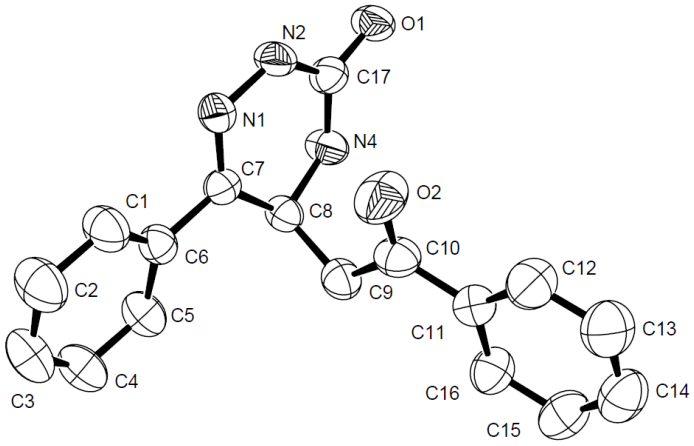
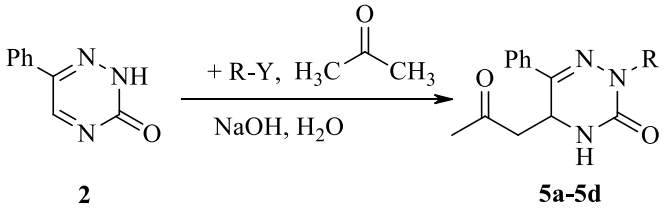


Figure 1. ORTEP diagram of **4e**.[17a]

Treatment of 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** with alkyl halides in aqueous acetone and in the presence of sodium hydroxide formed 2-alkyl-5-(2-oxopropyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **5a**–**d** resulting both from alkylation and from addition of acetone at positions 2 and 5, respectively (Table 3, Figure 2). Under the same conditions, 5-phenylpyrimidin-2(1*H*)-one **1a** did not react with acetone.

Table 3. Reaction of **2** with alkyl halides and acetone forming alkylated addition products **5a**–**d**



2 **5a-5d**

R	Y	R–Y [equiv.]	Product	Yield [%]
CH_3	I	10	**5a**	34
CH_3CH_2	I	2	**5b**	38
$CH_3CH_2CH_2$	Br	1.2	**5c**	12
$PhCH_2$	Cl	1.2	**5d**	14

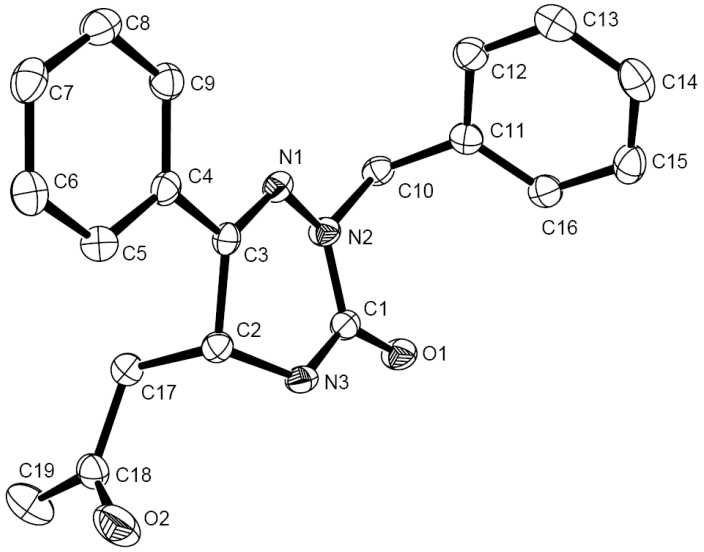


Figure 2. ORTEP diagram of **5d**.[17b]

It should be noted that 6-phenyl-1,2,4-triazin-3(2*H*)-one **2** adds N-nucleophiles[11] and O-nucleophiles.[12a] By contrast, 5-phenylpyrimidin-2(1*H*)-one **1a** did not react with cyclic amines (morpholine, piperidine) neither upon heating with pure amines nor in the presence of sulfur as oxidant; **1a** is also unreactive toward aliphatic alcohols both under basic and acidic conditions (in the presence of triethylamine and trifluoroacetic acid, respectively).

Experimental Section

General. 1b[18] and **2a**[19] were synthesized by known methods; other reactants are commercially available. TLC analysis was performed on Merck silica gel $60F_{254}$ plates and visualized by exposure to UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer, using tetramethylsilane (TMS) as an internal standard. X-Ray analysis including data collection, cell refinement and data reduction was carried out with an Oxford Diffraction Xcalibur S CCD diffractometer using CrysAlisPro software package.[20] The structures were resolved using SHELXS-97 and refined by full-matrix least-squares procedure on F^2 with SHELXL-97.[21]

5-Phenyl-2(1*H*)-pyrimidinone (1a). A mixture of phenylmalondialdehyde hydrate (1.50 g, 9 mmol), urea (1.084 g, 18 mmol) and *p*-toluenesulfonic acid (100 mg) was dissolved in toluene (50 mL) and refluxed using a Dean-Stark trap for 40 min. Then, toluene was decanted and the insoluble gummy residue was crystallized from ethanol to give a white powder **1a** (0.62 g, 40%); mp 239 ºC (lit.[22] mp 237 °C). ^{1}H NMR (400 MHz, DMSO-d_6□: δ 7.28–7.31 (m, 1H, Ph), 7.38–7.42 (m, 2H, Ph), 7.53–7.55 (m, 2H, Ph), 8.51 (s, 2H), 12.14 (s, 1H, NH). ^{1}H NMR spectral data correspond to those given in the literature.[23]

General procedure for the synthesis of (3) and (4a–c)
To a suspension of **1a**,**b** or **2** (150 mg) in chloroform (5 mL) was added trifluoroacetic acid (100 μL) and the nucleophilic reactant (1.1 equiv.). The mixture was stirred at ambient temperature for 18 h. Then, triethylamine (100 μL) was added, the mixture was evaporated, and the residue was crystallized from ethanol.
4-(1*H*-Indol-3-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3aa). 1a (150 mg, 0.871 mmol) and indole (112 mg, 0.956 mmol) gave grey crystals **3aa** (71 mg, 28%). Alternatively, the reaction was carried out in acetic acid (5 mL) and refluxed for 1–3 h affording **3aa** (106 mg, 42%); mp 248–249 °C. R_f = 0.45 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 55.63 (d, *J* = 2.8 Hz, 1H), 6.74 (d, *J* = 5.3 Hz, 1H), 6.95–7.04 (m, 3H), 7.06–7.14 (m, 4H), 7.24–7.26 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.52 (d, *J* = 3.6 Hz, 1H, NH), 10.75 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 48.9, 110.5, 111.5, 117.1, 118.6, 119.2, 121.0, 122.5, 123.6, 124.0, 125.1, 125.3, 128.2, 136.6, 136.7, 152.8. Anal. found: C, 74.75; H, 5.34; N, 14.43. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52.
4-(1-Methyl-1*H*-indol-3-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3ab). 1a (150 mg, 0.871 mmol) and 1-methylindole (126 mg, 0.961 mmol) gave yellow crystals **3ab** (111 mg, 42%); mp 289–290 °C. R_f = 0.4 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, NCH_3), 5.61 (d, *J* = 2.8 Hz, 1H), 6.75 (d, *J* = 5.4 Hz, 1H), 6.99–7.06 (m, 3H), 7.08–7.18 (m, 4H), 7.24–7.30 (m, 3H), 7.78 (d, *J* = 7.9 Hz, 1H), 8.53 (d, *J* = 3.8 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.2, 48.5, 109.7, 110.5, 116.3, 118.7, 119.4, 121.2, 122.7, 123.9, 125.4, 125.5,

127.7, 128.2, 136.6, 137.0, 152.8. Anal. found: C, 75.20; H, 5.73; N, 13.66. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85.

4-(2-Methyl-1*H*-indol-3-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3ac). 1a (150 mg, 0.871 mmol) and 2-methylindole (126 mg, 0.961 mmol) gave grey crystals **3ac** (145 mg, 55%); mp 239–240 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 5.73 (d, J = 1.8 Hz, 1H), 6.58 (d, J = 5.3 Hz, 1H), 6.80 (s, 1H), 6.84–6.93 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 7.7 Hz, 2H), 7.14-7.19 (m, 3H), 7.56 (d, J = 7.8 Hz, 1H), 8.51 (d, J = 3.9 Hz, 1H, NH), 10.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.9, 49.1, 110.5, 110.9, 113.7, 118.9, 119.0, 120.5, 122.9, 124.6, 125.9, 126.9, 128.6, 133.0, 135.7, 137.7, 152.9. Anal. found: C, 75.05; H, 5.73; N, 13.96. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85.

4-(1-Methyl-1*H*-pyrrol-2-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3ad). 1a (150 mg, 0.871 mmol) and *N*-pyrrole (71 mg, 0.958 mmol) gave grey crystals **3ad** (62 mg, 28%); mp 205–206 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.55 (s, 3H, NCH_3), 5.14 (d, J = 2.9 Hz, 1H), 5.95 (t, J = 2.2 Hz, 1H), 6.47 (d, J = 2.2 Hz, 2H), 6.65 (d, J = 5.3 Hz, 1H), 6.94 (s, 1H), 7.04 (t, J = 7.3 Hz, 1H), 7.17 (t, J = 7.8 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 8.34 (d, J = 3.6 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.5, 49.1, 106.5, 111.8, 118.9, 121.7, 122.2, 123.7, 125.3, 126.3, 128.3, 136.7, 153.3. Anal. found: C, 71.32; H, 5.88; N, 16.74. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59.

1-Methyl-4-(1*H*-indol-3-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3ba). 1b (150 mg, 0.806 mmol) and indole (104 mg, 0.888 mmol) gave colorless crystals **3ba** (222 mg, 84%). The reaction was also carried out in a mixture of methylene chloride (5 mL), ethanol (2 mL), and trifluoromethanesulfonic acid (100 μL) with stirring for 18 h to furnish **3ba** (217 mg, 82%); mp 174 °C. R_f = 0.4 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6□): δ 2.78 (s, 3H, NCH_3), 5.63 (s, 1H), 6.69 (d, J = 5.3 Hz, 1H), 6.95–7.05 (m, 3H), 7.12 (t, J = 7.7 Hz, 2H), 7.25–7.31 (m, 4H), 7.67 (d, J = 7.9 Hz, 1H), 8.74 (d, J = 5.3 Hz, 1H, NH), 10.89 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.1, 55.8, 110.6, 111.7, 113.7, 118.88, 118.90, 121.0, 121.6, 123.9, 125.0, 125.3, 125.4, 128.1, 136.4, 136.5, 152.4. Anal. found: C, 75.02; H, 5.57; N, 13.91. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85.

1-Methyl-4-(1-methyl-1*H*-indol-3-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3bb). 1b (150 mg, 0.806 mmol) and 1-methylindole (116 mg, 0.886 mmol) gave colorless crystals **3bb** (202 mg, 73%); mp 207–208 °C. R_f = 0.45 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6□: δ 2.78 (s, 3H, NCH_3), 3.73 (s, 3H, NCH_3), 5.62 (s, 1H), 6.70 (d, J = 5.4 Hz, 1H), 6.97–7.03 (m, 2H), 7.09–7.13 (m, 3H), 7.24–7.30 (m, 4H), 7.70 (d, J = 8.0 Hz, 1H), 8.75 (d, J = 5.3 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.2, 32.3, 55.3, 109.9, 110.7, 113.0, 119.0, 119.1, 121.2, 121.7, 123.9, 125.4, 125.8, 128.2, 129.0, 136.4, 136.8, 152.4. Anal. found: C, 75.58; H, 6.28; N, 12.96. Calcd. for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24.

1-Methyl-4-(2-methyl-1*H*-indol-3-yl)-5-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3bc). 1b (150 mg, 0.806 mmol) and 2-methylindole (116 mg, 0.886 mmol) gave grey crystals **3bc** (138 mg, 50%); mp 276 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44 (s, 3H, CH_3), 2.67 (s, 3H, NCH_3), 5.70 (s, 1H), 6.57 (d, J = 5.3 Hz, 1H), 6.87–6.95 (m, 2H), 6.96–6.70 (m, 1H), 7.08–7.12 (m, 2H),

7.16–7.20 (m, 3H), 7.54 (d, *J* = 7.6 Hz, 1H), 8.72 (d, *J* = 5.3 Hz, 1H, NH), 10.71 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.3, 31.4, 55.1, 109.5, 109.9, 110.6, 118.2, 118.6, 120.1, 121.7, 124.1, 125.5, 128.1, 133.7, 135.3, 137.0, 152.1. Anal. found: C, 75.43; H, 5.96; N, 13.23. Calcd. for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24.

5-(1*H*-Indol-3-yl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4a). 2 (150 mg, 0.866 mmol) and indole (112 mg, 0.953 mmol) gave colorless crystals **4a** (121 mg, 48%). The reaction was carried out under varied conditions: In a mixture of methylene chloride (5 mL) and ethanol (2 mL) with stirring for 18 h, no product was formed; refluxing in DMF (3 mL) for 1–3 h formed **4a** (189 mg, 75%); refluxing in acetic acid (5 mL) for 1–3 h provided **4a** (216 mg, 86%). Stirring in acetic acid (5 mL) in the presence of $Co(OTf)_2$ (31 mg, 0.087 mmol) at ambient temperature for 18 h followed by refluxing for 1 h furnished **4a** (38 mg, 15%); mp 272–273 °C. R_f = 0.45 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6□): δ 5.85 (d, *J* = 2.4 Hz, 1H, 5-H,), 6.99–7.05 (m, 2H), 7.09–7.10 (m, 1H), 7.23–7.26 (m, 3H, C_6H_5), 7.30–7.33 (m, 1H), 7.65-7.70 (m, 3H), 7.73 (br.s, 1H, NH, 4-H), 10.01 (br.s, 1H, NH, 2-H), 10.87 (br.s, 1H, NH). Anal. found: C, 70.21; H, 4.80; N, 19.46. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. ^{1}H NMR spectral data correspond to those given in the literature.[12b]

5-(1-Methyl-1*H*-indol-3-yl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4b). 2 (150 mg, 0.866 mmol) and 1-methylindole (125 mg, 0.953 mmol) gave colorless crystals **4b** (166 mg, 63 %); mp = 265–267 °C. R_f = 0.45 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6□): δ 3.68 (s, 3H, CH_3), 5.96 (d, *J* = 3.1 Hz, 1H, 5-H), 7.04–7.07 (m, 1H, indole), 7.13–7.17 (m, 1H, indole), 7.19 (s, 1H), 7.26–7.32 (m, 3H, Ph), 7.37 (d, *J* = 8.2 Hz, 1H), 7.69–7.74 (m, 3H), 7.84–7.85 (m, 1H), 10.27 (d, *J* = 2.0 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.8, 46.8, 110.4, 113.6, 119.58, 119.64, 122.0, 125.7, 126.0, 128.7, 128.9, 129.3, 134.7, 137.3, 143.4, 152.1. Anal. found: C, 71.02; H, 5.30; N, 18.51. Calcd. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. NMR spectral data correspond to those given in the literature.[12b]

5-(2-Methyl-1*H*-indol-3-yl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4c). 2 (150 mg, 0.866 mmol) and 2-methylindole (125 mg, 0.953 mmol) gave colorless crystals **4c** (127 mg, 48 %); mp 275–276 °C. R_f = 0.4 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6□): δ 2.46 (s, 3H, CH_3), 5.99 (d, *J* = 2.3 Hz, 1H, 5-H), 6.91–6.99 (m, 2H, indole), 7.20–7.28 (m, 4H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.59–7.62 (m, 3H), 10.32 (d, *J* = 1.7 Hz, 1H, NH), 10.99 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.8, 47.1, 111.1, 111.4, 118.3, 119.4, 120.9, 125.9, 126.3, 128.7, 129.1, 134.0, 135.3, 135.6, 142.4, 151.2. Anal. found: C, 71.30; H, 5.30; N, 18.48. Calcd. for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. NMR spectral data correspond to those given in the literature.[12b]

General method for the preparation of (4d–g)

A mixture of 6-phenyl-1,2,4-triazin-3(2*H*)-one (**2**, 200 mg, 1.15 mmol), the nucleophilic reactant (1.1 mmol equiv.), and BF_3•OMe_2 (145 μL, 1.15 mmol) in acetic acid (5 mL) was refluxed for 1–3 h. The reaction was monitored by TLC. The reaction mixture was evaporated in vacuo; the gummy residue was crystallized from ethanol.

6-Phenyl-5-(thiophen-2-yl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4d). **2** and thiophene (107 mg, 1.27 mmol) gave cream colored crystals **4d** (122 mg, 41%); mp 250–251 °C. ^{1}H NMR (400 MHz, DMSO-d_6□): δ 6.03 (d, *J* = 3.1 Hz, 1H, 5-H), 6.87–6.97 (m, 1H, thiophene), 7.01 (d, *J* = 2.8 Hz, 1H, thiophene), 7.36–7.42 (m, 4H, Ph, thiophene), 7.76–7.78 (m, 2H, Ph), 8.16 (s, 1H, NH), 10.34 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 49.0, 126.2, 126.3, 126.8, 127.4, 129.1, 129.7, 134.0, 143.3, 143.7, 152.0. Anal. found: C, 60.74; H, 4.40; N, 16.45. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33.

5-(2-Oxo-2-phenylethyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4e). **2** and acetophenone (153 mg, 1.27 mmol) gave cream colored crystals **4e** (200 mg, 59%); mp 204 °C. R_f = 0.7 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6)□: δ 2.99 (dd, *J* = 17.2, 2.9 Hz, 1H), 3.55 (dd, *J* = 17.2, 9.2 Hz, 1H), 5.17 (dt, *J* = 3.6, 5.1 Hz, 1H, 5-H), 7.25–7.30 (m, 1H), 7.32–7.41 (m, 3H), 7.45–7.49 (m, 2H), 7.56–7.62 (m, 1H), 7.66–7.75 (m, 2H), 7.91–7.94 (m, 2H), 10.04 (d, *J* = 2.2 Hz, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 40.9, 46.2, 125.4, 128.2, 128.7, 129.3, 133.3, 133.5, 136.5, 143.6, 151.9, 196.8. Anal. found: C, 69.75; H, 5.12; N, 14.43. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33.

5-[2-Oxo-2-(thiophen-2-yl)ethyl]-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4f). **2** and 2-acetothienone (160 mg, 1.27 mmol) gave cream colored crystals **4f** (142 mg, 41%); mp 205–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6□): δ 2.95–3.03 (m, 1H), 3.36–3.46 (m, 1H), 5.15 (m, 1H, 5-H), 7.18–7.22 (m, 1H), 7.38–7.45 (m, 3H), 7.57 (br.s, 1H), 7.68–7.72 (m, 2H), 7.87-7.90 (m, 1H), 7.97-7.99 (m, 1H), 10.11 (br.s, 1H). Anal. found: C, 60.32; H, 4.44; N, 14.17. Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04.

5-(2-Oxopropyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4g). **2** and acetone (74 mg, 1.27 mmol) gave colorless crystals **4g** (112 mg, 42%); mp 141 °C. R_f = 0.45 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3), 2.50–2.53 (m, 1H), 2.87 (dd, *J* = 16.6, 9.6 Hz, 1H), 4.90–5.04 (m, 1H, 5-H), 7.21–7.29 (m, 1H, NH), 7.30–7.43 (m, 3H, Ph), 7.66–7.69 (m, 2H, Ph), 9.99 (d, *J* = 2.1 Hz, 1H, NH). Anal. found: C, 62.38; H, 5.76; N, 18.29. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. NMR spectral data correspond to those given in the literature.[12a]

General procedure for the synthesis of 2-alkyl-5-(2-oxopropyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones (5a–d)

Acetone (5 mL) was added to a suspension of 6-phenyl-1,2,4-triazin-3(2*H*)-one (**2**, 1.00 g, 5.77 mmol) in aqueous NaOH (2N, 5 mL). To the resulting solution was added the appropriate alkyl halide (see Table 3). After stirring for 24 h, the precipitate formed was filtered off and crystallized from acetonitrile.

2-Methyl-5-(2-oxopropyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (5a). **2** and methyl iodide gave colorless crystals **5a** (482 mg, 34%); mp 136–137 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.14 (s, 3H, CH_3CO), 2.49–2.54 (m, 1H, CH), 2.82–2.89 (m, 1H, CH), 3.29 (s, 3H, NCH_3), 4.96–5.00 (m, 1H, CH, 5-H), 7.35–7.40 (m, 4H, Ph), 7.68–7.70 (m, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.3, 37.0, 45.3, 46.1, 125.4, 128.7, 129.4, 132.6, 143.9, 151.7, 205.4. Anal. found: C 63.62; H 5.98; N 17.05. Calcd. for $C_{13}H_{15}N_3O_2$: C 63.66; H 6.16; N 17.13.

2-Ethyl-5-(2-oxopropyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (5b). **2** and ethyl iodide gave colorless crystals **5b** (569 mg, 38%); mp 146–147 °C. ^{1}H NMR (400 MHz, DMSO-d_6□: δ 1.17 (t, *J* = 6.9 Hz, 3H, CH_3), 2.12 (s, 3H, CH_3CO), 2.56 (dd, *J* = 16.3, 2.1 Hz, 1H, CH), 2.80 (dd, *J* = 16.4, 9.2 Hz, 1H, CH), 3.64–3.72 (m, 2H, NCH_2), 4.98–5.00 (m, 1H, 5-H), 7.42–7.44 (m, 3H, Ph), 7.51 (d, *J* = 3.2 Hz, 1H, NH), 7.71–7.73 (m, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.3, 30.3, 43.3, 45.4, 46.0, 125.4, 128.7, 129.4, 132.8, 143.9, 151.0, 205.4. Anal. found: C 64.88; H 6.77; N 16.07. Calcd. for $C_{14}H_{17}N_3O_2$: C 64.85; H 6.61; N 16.20.

5-(2-Oxopropyl)-6-phenyl-2-propyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (5c). **2** and propyl bromide gave colorless crystals **5c** (190 mg, 12%); mp 129–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6□: δ 0.89 (t, *J* = 7.4 Hz, 3H, CH_3), 1.60–1.69 (m, 2H, CH_2), 2.12 (s, 3H, $COCH_3$), 2.57 (dd, *J* = 16.4, 3.1 Hz, 1H, CH), 2.78 (dd, *J* = 16.4, 9.1 Hz, 1H, CH), 3.51-3.71 (m, 2H, CH_2), 4.99 (td, *J* = 9.1, 3.5, 3.5 Hz, 1H, 5-H), 7.36–7.46 (m, 3H, Ph), 7.49 (d, *J* = 3.8 Hz, 1H, NH), 7.70–7.72 (m, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.0, 21.2, 30.3, 45.6, 46.0, 49.8, 125.4, 128.7, 129.3, 132.8, 143.6, 151.0, 205.4. Anal. found: C 65.82; H 7.13; N 15.49. Calcd. for $C_{15}H_{19}N_3O_2$: C 65.91; H 7.01; N 15.37.

2-Benzyl-5-(2-oxopropyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (5d). **2** and benzyl chloride gave colorless crystals **5d** (260 mg, 14%); mp 162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.14 (s, 3H, $COCH_3$), 2.56 (dd, *J* = 16.6, 2.9 Hz, 1H, CH), 2.84 (dd, *J* = 16.6, 9.4 Hz, 1H, CH), 4.80–4.92 (m, 2H, CH_2), 5.02 (td, *J* = 9.3, 3.1, 3.1 Hz, 1H, 5-H), 7.17–7.25 (m, 1H, Ph), 7.26–7.40 (m, 7H, Ph), 7.44 (d, *J* = 3.7 Hz, 1H, NH), 7.65–7.67 (m, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.3, 45.8, 46.2, 51.8, 125.4, 126.8, 127.6, 128.2, 128.7, 129.5, 132.6, 138.6, 144.1, 151.1, 205.3. Anal. found: C 71.32; H 5.84; N 13.11. Calcd. for $C_{19}H_{19}N_3O_2$: C 71.01; H 5.96; N 13.08. ^{1}H NMR spectral data correspond to those given in the literature.[12a]

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