Synthesis of Novel Spiropyrimidinones

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An efficient one-pot synthesis of new spirocyclic 2-aminopyrimidinones *via* the three-component reaction of a cyclic ketone, alkyl cyanoacetate, and guanidinium carbonate was developed *via* a domino reaction.

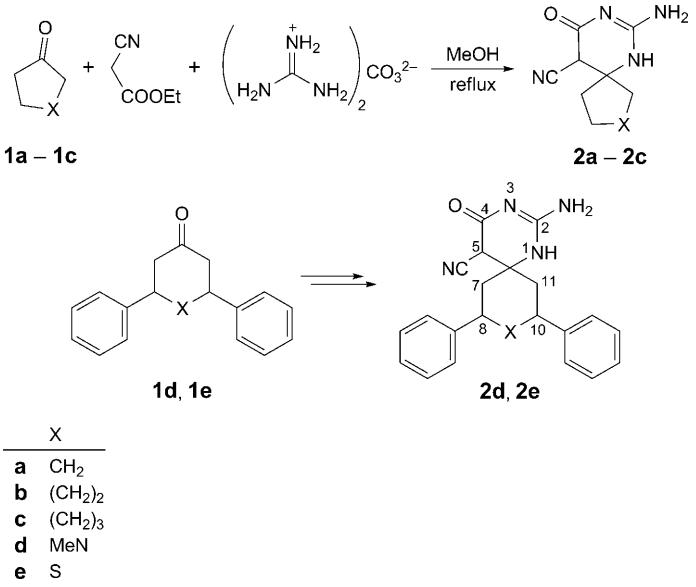
Introduction. – The development of efficient and mild methods for heterocyclic-compound synthesis represents a broad area of organic chemistry [1]. Compounds containing such units play an essential role because of their biological activity. Among those heterocycles, pyrimidine derivatives are important because they are the parent compounds of numerous pyrimidine nucleobases and enzymes [2]. Pyrimidinones and their derivatives have emerged in recent years as candidates for drugs due to their anticancer [3], anti-HIV [4], central-stimulant [5], calcium-antagonist [6], antihypertensive [7], and anti-inflammatory properties [8], and are rendered as valuable agrochemicals [9]. Additionally, their structure has been found in the natural marine alkaloids batzelladine A and B, which inhibit the binding of HIV gp-120 to CD_4 cells, so disclosing a new field towards the development of AIDS therapy [10]. On the other hand, spiro heterocycles have promising biological activity, such as antidepressant [11], neuroleptic [12] and hypotensive activity [13], as tryptase inhibitors [14], *etc.*

Pursuing our research on pyrimidine derivatives [15], we describe herein a method for synthesizing spirocyclic 2-aminopyrimidinones. In this context, we made an attempt to synthesize the target compounds *via* a domino reaction. This method includes the reaction of a cyclic ketone, guanidinium carbonate, and ethyl cyanoacetate under mild conditions to give the corresponding spiro compounds in good yield *via* a domino *Knoevenagel–Michael* addition–cyclocondensation reaction.

Results and Discussion. – In this approach, we synthesized spiropyrimidinones **2a**–**2c** within a short span of 1–3 h from various cycloalkanones **1a**–**1c**, ethyl cyanoacetate, and guanidinium carbonate (*Scheme 1*). Also, we extended this method to heterocyclic ketones **1d** and **1e** instead of cycloalkanones as starting carbonyl compounds. It was found that the reaction proceeds smoothly with high yield. The heterocyclic ketones **1d** and **1e** were prepared adopting described methods [16][17].

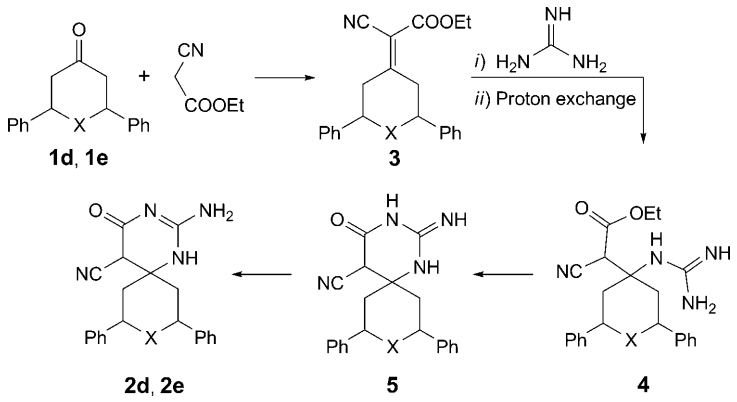
The proposed protocol involves the formation of an alkene intermediate **3** *via* a *Knoevenagel* reaction (*Scheme 2*). The formation of the alkene intermediate is confirmed by comparing the TLC of the three-component reaction mixture with that of a reaction mixture of only the cyclic ketone and ethyl cyanoacetate. The alkene acts as a

Scheme 1



Michael acceptor, and the free guanidine which is obtained by refluxing guanidinium carbonate in MeOH adds to the alkene. The desired spiropyrimidinone is obtained by cyclization *via* intermediates **4** and **5** by a domino *Michael* addition–cyclocondensation reaction (*Scheme 2*). By this methodology, the synthesis of spirocyclic 2-amino-pyrimidinones is completed within 1–3 h in very high yields. The structure of the products were supported by spectroscopic and analytical data.

Scheme 2. *Mechanism of the Synthesis of Spiropyrimidinones*

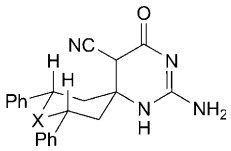


The IR spectrum of the spirocyclic 2-aminopyrimidinones **2** displays characteristic absorption bands in the region of 2160–2200 (C≡N stretching) and 3140–3390 cm^{-1} (NH stretching) and a peak around 1665 cm^{-1} (C=O stretching). In the ^{1}H-NMR

spectra, a *s* in the region of δ 3.7–4.1 was assigned to H–C(5) of the pyrimidinone ring. In the ^{13}C-NMR spectra, the quaternary C(6) (spiro C-atom) appeared between δ 53.0 and 61.7. The nitrile and C=O C-atoms resonated around δ 117 and 168, respectively.

In **2d** the axial and equatorial protons CH_2(7) and CH_2(11) of the piperidine ring appear as a *m* in the region of δ 1.6–1.8, and the benzylic H–C(8) and H–C(10) as *dd* at δ 3.48 ($J_{trans} = 11.5$ and $J_{cis} = 2.5$ Hz) and 3.43 ($J_{trans} = 12.5$ and $J_{cis} = 3$ Hz), respectively. The observed coupling constants are typical *vicinal* coupling constants J_{anti} and J_{gauche} in the chair conformation [18]. This suggests the axial nature of H–C(8) and H–C(10), *i.e.*, the equatorial orientation of the Ph groups at C(8) and C(10). Thus, the ^{1}H-NMR spectra reveals that the two Ph groups have a *cis* relationship with respect to each other.

Comparison of the coupling constant of **2d** with the parent **1d** [19] ($J_{trans} = 11$ and $J_{cis} = 3.5$ Hz) reveals that in **2d**, the *trans* coupling is greater, whereas the *cis* coupling is smaller. This suggests that the ring is flattened about C(2)–C(3) and C(5)–C(6) bonds in the parent compound **1d** relative to **2d**. Distortion from flattening to ideal chair generally increases J_{trans} and decreases J_{cis} [20]. Similar effects were observed for **2e** (*Fig.*).



X = MeN, S

Figure. *Chair conformation of* **2d** *and* **2e**

In conclusion, the reported protocol is an efficient synthetic route to spirocyclic 2-aminopyrimidinones based on a three-component condensation of a cyclic ketone with ethyl cyanoacetate and guanidinium carbonate. This methodology involves two (or) more bond-forming transformations which take place under the same reaction conditions without adding additional reagents or catalysts (domino *Knoevenagel–Michael* addition–cyclocondensation reaction). Also the reaction has several advantages like mild reaction conditions, no chemical waste, and no product purifications.

Experimental Part

General. M.p.: in open capillary; uncorrected. FT-IR Spectra: *Nicolet-Avatar-360-FT-IR* instrument; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-AMX-400* and *Bruker-AMX-500* spectrometers; in (D_6)DMSO; δ in ppm rel. to Me_4Si, *J* in Hz. MS: *Varian-GC-MS-Saturn-2200-Thermo* instrument; capillary column *Vf5MS*; CI mode with CH_4; samples diluted in MeOH. Elemental analysis: *Vario-EL.-CHNS* elemental analyzer.

Spirocyclic 2-Aminopyrimidinones: General Procedure. Procedure exemplified for **2a**–**2e**: A soln. of guanidinium carbonate (1.5 mmol) in MeOH (20 ml) was heated under reflux for 15 min. After the mixture had cooled to r.t., cyclic ketone **1** (1 mmol) and ethyl cyanoacetate (1.2 mmol) were added, and the mixture was heated under reflux (TLC (MeOH/AcOEt 1:10) monitoring). After completion of the reaction, the solid products were collected by filtration and washed with cold H_2O to remove excess guanidinium carbonate.

2-Amino-4-oxo-1,3-diazaspiro[5.4]dec-2-ene-5-carbonitrile (**2a**): Yield 160.5 mg (83.6%). M.p. 280–283°. IR (KBr): 3380 (NH asym.), 3315 (NH sym.), 2163 (C≡N), 1699 (C=O), 1590 (C=N). ^{1}H-NMR ((D$_6$)DMSO): 7.89 (*s*, NH); 6.61 (*s*, NH$_2$); 3.92 (*s*, H–C(5)); 1.62–1.69 (*m*, 8 H). ^{13}C-NMR ((D$_6$)DMSO): 168.4 (C=O); 160.6 (C(2)); 117.0 (C≡N); 61.7 (C(6)); 43.0 (C(5)); 36.9; 35.4; 23.2; 23.10. MS: 193.1 ([*M* + 1]$^+$). Anal. calc. for $C_9H_{12}N_4O$: C 56.24, H 6.29, N 29.15; found: C 56.01, H 6.17, N 29.05.

2-Amino-4-oxo-1,3-diazaspiro[5.5]undec-2-ene-5-carbonitrile (**2b**): Yield 175.3 mg (85.1%). M.p. 295–298°. IR (KBr): 3393 (NH asym.), 3321 (NH sym.), 2166 (C≡N), 1663 (C=O), 1585 (C=N). ^{1}H-NMR ((D$_6$)DMSO): 7.61 (*s*, NH); 3.85 (*s*, H–C(5)); 1.40–1.60 (*m*, 10 H). ^{13}C-NMR ((D$_6$)DMSO): 167.8 (C=O); 160.1 (C(2)); 116.8 (C≡N); 53.2 (C(6)); 44.9 (C(5)); 40.1; 34.1; 31.5; 24.3; 20.4. MS: 206.2 (*M*$^+$). Anal. calc. for $C_{10}H_{14}N_4O$: C 58.24, H 6.84, N 27.17; found: C 57.93, H 6.59, N 27.10.

2-Amino-4-oxo-1,3-diazaspiro[5.6]dodec-2-ene-5-carbonitrile (**2c**): Yield 174.2 mg (79.2%). M.p. 286–291°. IR (KBr): 3358 (NH asym.), 3319 (NH sym.), 2160 (C≡N), 1671 (C=O), 1589 (C=N). ^{1}H-NMR ((D$_6$)DMSO): 7.7 (*s*, NH); 6.5 (*s*, NH$_2$); 3.86 (*s*, H–C(5)); 1.3–1.8 (*m*, 12 H). ^{13}C-NMR ((D$_6$)DMSO): 168.2 (C=O); 160.1 (C(2)); 117.5 (C≡N); 56.7 (C(6)); 45.8 (C(5)); 40.1; 34.8; 28.3; 28.2; 21.3; 21.0. MS: 220.9 ([*M* + 1]$^+$). Anal. calc. for $C_{11}H_{16}N_4O$: C 69.98, H 7.32, N 25.44; found: C 69.44, H 7.14, N 25.03.

2-Amino-9-methyl-4-oxo-8,10-diphenyl-1,3,9-triazaspiro[5.5]undec-2-ene-5-carbonitrile (**2d**): Yield 281.2 mg (75.4%). M.p. 263–265°. IR (KBr): 3357 (NH asym.), 3306 (NH sym.), 2164 (C≡N), 1668 (C=O), 1579 (C=N). ^{1}H-NMR ((D$_6$)DMSO): 8.2 (*s*, NH); 7.2–7.3 (*m*, 10 arom. H, NH$_2$); 3.9 (*s*, H–C(5)); 3.48 (*dd*, *J* = 11.5, 2.5, H–C(8)); 3.43 (*dd*, *J* = 12.5, 3, H–C(10)); 1.6–1.8 (*m*, CH$_2$(7), CH$_2$(11)); 1.72 (*s*, MeN). ^{13}C-NMR ((D$_6$)DMSO): 167.5 (C=O); 160.1 (C(2)); 143.7; 143.6; 126.9–128.7; 116.4 (C≡); 64.1 (C(10)); 63.7 (C(8)); 53.0 (C(6)); 44.5 (C(5)); 43.3 (C(11)); 41.2 (C(7)); 40.8 (MeN). MS: 373.1 (*M*$^+$). Anal. calc. for $C_{22}H_{23}N_5O$: C 70.76, H 6.21, N 18.75; found: C 70.41, H 5.97, N 18.53.

2-Amino-4-oxo-8,10-diphenyl-9-thia-1,3-diazaspiro[5.5]undec-2-ene-5-carbonitrile (**2e**): Yield 296.2 mg (78.8%). M.p. 250–254°. IR (KBr): 3353 (NH asym.), 3315 (NH sym.), 2163 (C≡N), 1667 (C=O), 1580 (C=N). ^{1}H-NMR ((D$_6$)DMSO): 8.1 (*s*, NH); 7.3–7.4 (*m*, 10 arom. H, NH$_2$); 4.46 (*dd*, *J* = 12.5, 2.5, H–C(8)); 4.35 (*dd*, *J* = 11.5, 3.5, H–C(10)); 4.1 (*s*, H–C(5)); 2.0–2.2 (*m*, CH$_2$(7), CH$_2$(11)). ^{13}C-NMR ((D$_6$)DMSO): 167.4 (C=O); 160.1 (C(2)); 140.0; 127.3–128.9; 116.4 (C≡N); 54.8 (C(6)); 45.5 (C(5)); 42.3 (C(10)); 41.9 (C(8)). MS: 376.4 (*M*$^+$). Anal. calc. for $C_{21}H_{20}N_4OS$: C 67.00, H 5.35, N 14.88; found: C 66.74, H 5.02, N 14.60.

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