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A novel and efficient domino reaction for the one-pot synthesis of spiro-2-aminopyrimidinones

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Abstract

A novel and efficient protocol is developed for the synthesis of various spiro-2-amino pyrimidinones via the three-component condensation of alkyl cyanoacetates, guanidinium carbonate and N-substituted 4-piperidinones in ethanol at reflux. High yields, neutral conditions, and short reaction times are advantages of this method.

Keywords: One-pot three-component reaction; Spiro-2-aminopyrimidinones; Domino reaction; Domino Knoevenagel-cyclocondensation; Neutral conditions; Guanidinium carbonate

There are many natural and biologically active compounds that contain ring systems connected to each other through a spiro carbon atom. The aza-spirocyclic system is present in some alkaloids with anti-leukemic activity such as pinnaic acid, halichlorine, cephalotaxine, and its ester derivative.[1–3] Compounds with spiro skeletons not only constitute subunits in numerous alkaloids, but are also templates for drug discovery and have been used as scaffolds for combinatorial libraries.[4] Spiro compounds display pronounced antitumor and antiviral activities and some have been shown to inhibit efficiently monoamine oxidase A and to bind with nanomolar affinity to secrotonin receptors in the central nervous system.[5,6]

One of the main synthetic challenges for the synthesis of novel alkaloids and related products is the selective construction of the spiro fragment. Several methods have been devised for solving this problem, for example, ring closing metathesis, rearrangement, and cycloaddition.[7]

2-Aminopyrimidinone derivatives have various biological activities and there is widespread interest in their synthesis because of this, along with their capacity to form hydrogen bonds and to undergo coagulation.[8]

Developing new environmentally benign and clean synthetic methods is important in organic synthesis. Domino reactions are such examples with high potential in organic synthesis. They have several advantages such as (a) rapid transformations, (b) minimizing the number of reaction steps and chemical waste, and (c) the occurrence of two or more bond-forming reactions under identical reaction conditions.[9]

Following our interest in using domino reactions for the synthesis of heterocyclic compounds,[10] we herein present a straightforward route for the synthesis of spiro-2-aminopyrimidinones via an efficient three-component reaction of N-substituted piperidinones, guanidinium carbonate, and alkyl cyanoacetates via a domino Knoevenagel-cyclocondensation reaction (Scheme 1).

Guanidinium carbonate was used as a source of free guanidine via refluxing methanol. This led to the formation of free guanidine within 15 min. This basic media was

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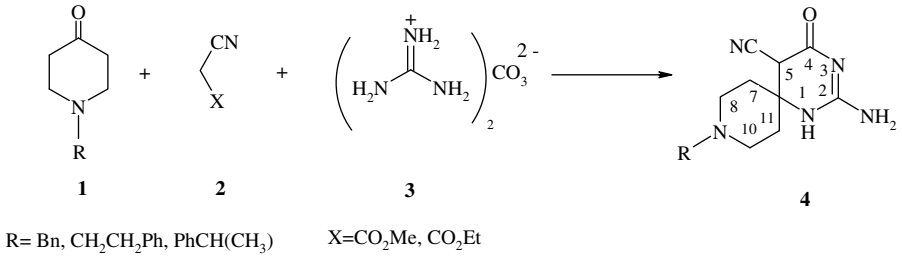


Scheme 1.

suitable for deprotonation of alkyl cyanoacetates **2** which on reaction with N-substituted piperidone **1** produced the desired alkene **5** through a Knoevenagel condensation. Formation of the alkene intermediate **5** was confirmed by the reaction of starting materials **1** and **2** in a separate vessel and comparison by TLC. Alkene **5** acts as a Michael acceptor and the reaction proceeds via a domino Knoevenagel-cyclocondensation reaction. The free guanidine probably adds to the alkene, and after cyclization, the desired spiro-2-aminopyrimidinone is formed (Scheme 2). The results obtained for the synthesis of spiro-2-aminopyrimidinones **4a**–**f** from various N-substituted 4-piperidinones are shown in Table 1.

The active carbonyl group in the *N*-alkyl-4-piperidinones makes them suitable starting materials for the synthesis of pharmaceutical compounds such as Fentanyl, Sufentanil, and the synthesis of spiro compounds with high σ_1 receptor affinity.

Formation of the spiro-2-aminopiperidinone structure was unambiguously supported by spectroscopic and analytical data. A singlet in the region δ 3.92–3.97 ppm in the ^{1}H NMR spectra was assigned to H-5 of the pyrimidinone ring. In the ^{13}C NMR spectra, the quaternary C-6 spiro carbon typically appeared between 60.0 and 64.3 ppm. The nitrile and carbonyl carbons resonated at ca. δ 117 and 168 ppm, respectively.[11]

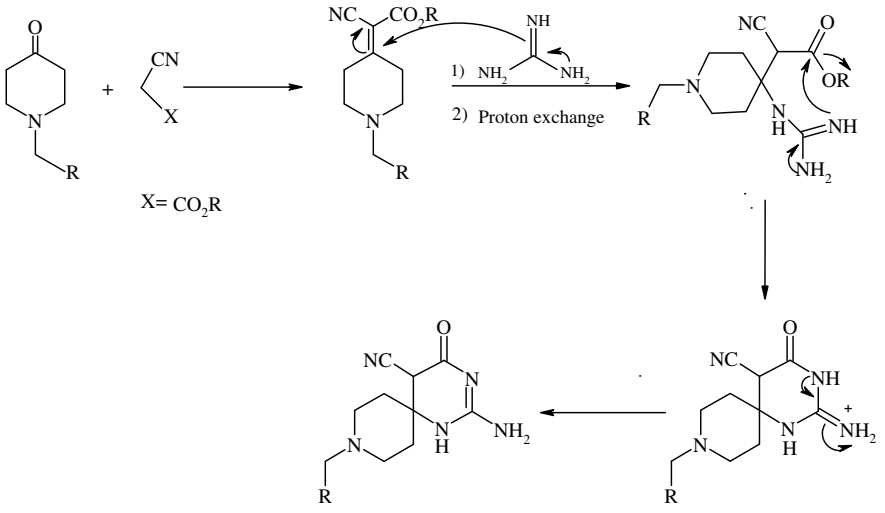
Table 1
Synthesis of spiro-2-amino pyrimidinones **4a**–**f**

R	X	Time (min)	Yield[a] (%)
Ph	CO_2Me	50	96
Ph	CO_2Et	45	95
CH_2-Ph	CO_2Me	30	94
CH_2-Ph	CO_2Et	20	96
(CH_3)–CH-Ph	CO_2Me	90	70[b]
(CH_3)–CH-Ph	CO_2Et	80	86[b]

[a] Yields refer to those of pure isolated products characterized by IR, ^{1}H, and ^{13}C NMR spectroscopy and CHN analysis data.
[b] Mixture of two diastereomers with a ratio of 1:1.

In all cases, for products **4a**–**f**, in the piperidine ring the axial and equatorial protons of H-7 and H-11 appeared as multiplets in the region 1.5–1.8 ppm. Meanwhile, H_{8ax} and H_{10ax} were observed as multiplets which were shielded compared to H_{8eq} and H_{10eq}. The equatorial hydrogens, H-8 and H-10, resonated at δ 2.1 ppm. When compound **1c** with a chiral center was used as starting material, products **4e** and **4f** were formed as mixtures of two diastereoisomers with a ratio of 1:1.

In conclusion, we have developed a novel domino Knoevenagel-cyclocondensation reaction for the synthesis of spiro-2-aminopyrimidinone in good to excellent yields with high purity and in short reaction times.



Scheme 2. The proposed mechanism for the synthesis of spiro-2-amino pyrimidinones **4a**–**f**.

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11. *General procedure for the preparation of compounds* **4a–f**: A solution of guanidinium carbonate (180 mg, 1.5 mmol) in methanol (20 ml) was heated under reflux for 15 min. After the mixture had cooled to room temperature, N-substituted piperidinone **1** (1 mmol) and alkyl cyanoacetate **2** (1.2 mmol) were added and the mixture heated under reflux. The progress of the reaction was monitored by TLC (EtOAc/methanol 10:1). After completion of the reaction, the solid product was collected by filtration and the solid washed with cold water to remove excess guanidinium carbonate.
Data for compounds **4a**, **4c**, and **4e**:
Compound **4a**: 2-Amino-9-benzyl-5-cyano-1,3,9-triazaspiro[5,5]-undeca-2-en-4-one Mp = 268–269 °C; IR (KBr, cm^{-1}): 3327, 3116, 2926, 2166, 1688, 1617, 1590; ^1H NMR (300 MHz, DMSO-d_6): δ 1.56–1.76 (m, 4H, H-$7_{ax,eq}$, H-$11_{ax,eq}$, $2CH_2$), 2.11–2.24 (m, 2H, H-8_{ax}, H-10_{ax}), 2.68 (m, 2H, H-8_{eq}, H-10_{eq}), 3.49 (s, 2H, $-CH_2N$), 3.95 (s, 1H, H-5), 6.40 (br s, 2H, NH_2), 7.32 (m, 5H, H-Ar), 7.74 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.96, 34.30, 45.02, 48.12, 48.28, 52.22, 62.40, 117.25, 127.45, 128.70, 129.18, 138.70, 160.55, 168.25; Anal. Calcd for $C_{16}H_{19}N_5O$: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.54; H, 6.34; N, 23.38.
Compound **4c**: 2-Amino-9-(2-phenylethyl)-5-cyano-1,3,9-triazaspiro-[5,5]undeca-2-en-4-one Mp = 264–265 °C; IR (KBr, cm^{-1}): 3394, 3312, 3108, 2926, 2166, 1663, 1611, 1581; ^1H NMR (300 MHz, DMSO-d_6): δ 1.56–1.73 (m, 4H, H-$7_{ax,eq}$, H-$11_{ax,eq}$, $2CH_2$), 2.14–2.27 (m, 2H, H-8_{ax}, H-10_{ax}), 2.52 (t, 2H, J = 6.9 Hz, $-CH_2Ph$), 2.72 (t, 2H, J = 6.9 Hz, $-CH_2N$), 2.77 (m, 2H, H-8_{eq}, H-10_{eq}), 3.97 (s, 1H, H-5), 6.70 (br s, 2H, NH_2), 7.16–7.26 (m, 5H, H-Ar), 7.90 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.97, 33.33, 34.26, 44.96, 48.11, 48.23, 52.31, 60.03, 117.19, 126.31, 128.71, 129.07, 140.81, 160.51, 168.44; Anal. Calcd for $C_{17}H_{21}N_5O$: C: 65.57, H: 6.79, N: 22.49. Found: C: 65.45, H: 6.79, N: 22.47.
Compound **4e**: Mixture of two diastereomers (1:1) 2-Amino-9-(*S*-1-phenylethyl)-5(*R* or *S*)-cyano-1,3,9-triazaspiro[5,5]undeca-2-en-4-one Mp = 271–273 °C; IR (KBr, cm^{-1}): 3420, 3311, 3132, 2931, 2171, 1668, 1615, and 1580; ^1H NMR (500 MHz, DMSO-d_6): δ 1.31 (d, 6H, J = 6.7 Hz, $2CH_3$), 1.60–1.67 (m, 8H, $H7_{ax,eq}$, H-$11_{ax,eq}$, 4 CH_2), 2.05–2.20 (m, 4H, H-8_{ax}, H-10_{ax}), 2.62 (m, 2H, H-8_{eq}, H-10_{eq} one diastereomer), 2.85 (m, 2H, H-8_{eq}, H-10_{veq} another diastereomer), 3.48 (q, 2H, J = 6.8 Hz, 2-CH), 3.91 (s, 1H, H-5), 3.93 (s, 1H, H-5), 6.20 (br s, 4H, $2NH_2$), 7.23–7.35 (m, 10H, H-Ar), 7.65 (br s, 2H, 2NH); ^{13}C NMR (75 MHz, DMSO-d_6) 45.99, 52.67, 64.29, 117.71, 127.72, 128.16, 129.14, 144.43, 160.94, and 168.57. Anal. Calcd for $C_{17}H_{21}N_5O$: C: 65.57, H: 6.79, N: 22.49. Found: C: 65.39, H: 6.79, N: 22.51.