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RESEARCH ARTICLE

Regioselective Synthesis of Spiro-2-aminopyrimidinone Derivatives in Ionic Liquid as Green Solvent

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Abstract: An interesting regioselectivity was investigated for the synthesis of spiro-2-aminopyrimidinones-5-carbonitrile **(4a-e)** by the multicomponent condensation of cyclic ketones **(1a-d)**, alkyl cyanoacetates **(2)** and various guanidine salts **(3)** using 3-butyl-1-methyl-1*H*-imidazol-3-ium tetrafluoroborate ([BMIM][BF_4]) as ionic liquid. Existence of two possible potentially active centers *i.e.* -CN and –COOR groups in the intermediate to Michael adduct results in possibility of formation of two region-isomeric products *i.e.* spiro-2-aminopyrimidinones-5-carbonitrile **(4a-e)** or spiro-2-amino-4-imino-pyrimidin-5-carboxylic acid alkyl ester **(5).** High regioselectivity was displayed with exclusive formation of compound **(4a-e)** which was further confirmed by spectral studies.

Keywords: Regioselectivity, Spiro-2-aminopyrimidinones-5-carbonitrile, Ionic liquid, Green solvent

Introduction

Recently, the growing awareness of environmental issues has focused attention on the need for greener and more sustainable technologies in the chemical industry[1]. The number of environmental laws and regulations has increased over the years and more specific regulations have been set in order to provide a safer environment. Thus the chemistry community has been mobilized to develop new chemistries that are less hazardous to human health and the environment. Green chemistry is not a part of the large field of chemistry, but it is a way of thinking and doing things better and more efficiently, because solvents are often necessary in chemical reactions, alternative solvents have been developed. The ideal solvent should have very low volatility, and it should be chemically and physically stable, recyclable, reusable and easy to handle. Therefore, one such candidate is an ionic liquid (IL)[2], which consist of cations and anions, have become an interesting research topic in the last decade, which is available in some books[3,4] and reviews[5,6] published about them. Many different ionic liquids have been prepared and they have successfully used as solvents in diverse reactions, such as Diels-Alder[7], Friedel-Crafts[8], Heck[9], hydration[10], oxidation[11], alkylation[12], allylation[13], hydroformulation[14], esterification[15], dimerization[16] and polymerization reactions[17] and enzyme catalysis[18], often leading to better selectivity, yield and reaction rates than with volatile organic solvents. ILs have a great variety of chemical and physical properties that can be tuned with cations and anions[19].

Organic molecules containing a spiro heterobicyclic moiety are of broad scientific interest due to their unique chemical and conformational features as well as the biological properties often associated with the asymmetric spiro carbon atom. They have attracted considerable attention from the synthetic community[20]. For example, new class of marine toxins isolated from shellfish and dinoflagellate, such as pinnatoxins and pteriatoxin[21], exhibits an azaspiro system responsible for the biological activity.

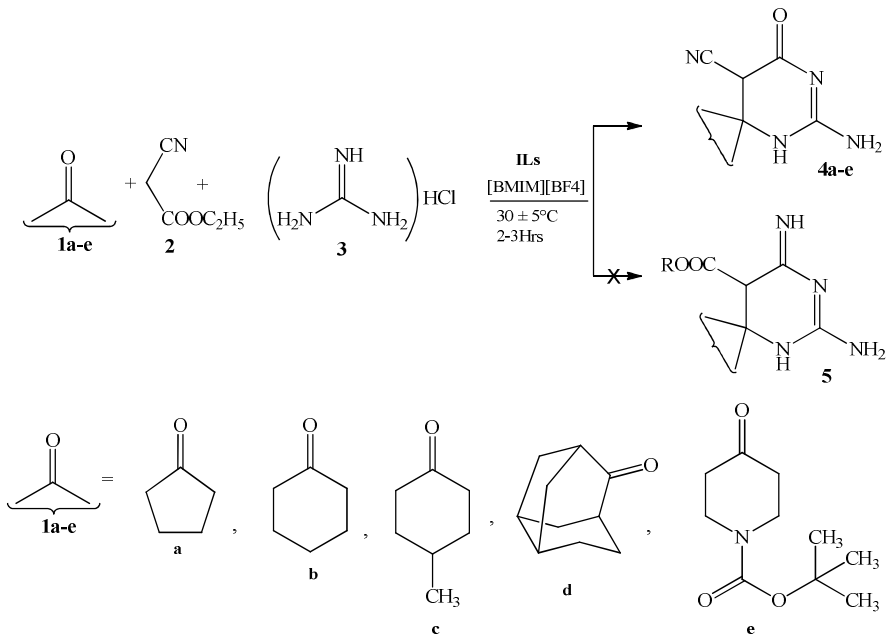
In addition, many spiro-compounds possess very promising biological activities as anticancer agents[22], antibacterial agents[23], anticonvulsant agents[24], anti-tuberculosis agents[25], anti-Alzheimer's agents[26], pain-relief agents[27], anti-dermatitis agents[28] and antimicrobial agents[29]. In addition to their medical uses, some spiro-compounds have found other uses in the agricultural and industrial fields. For example, they are used as antifungal agents[30], pesticides[31], laser dyes[32] and electroluminescent devices[33]. Spiro- compounds have also been recently used as antioxidants[34]. Hence, the synthesis of spiro-compounds incorporating privileged heterocycles could be a valuable strategy to discover new bioactive compounds in the context of chemical genomics.

Experimental

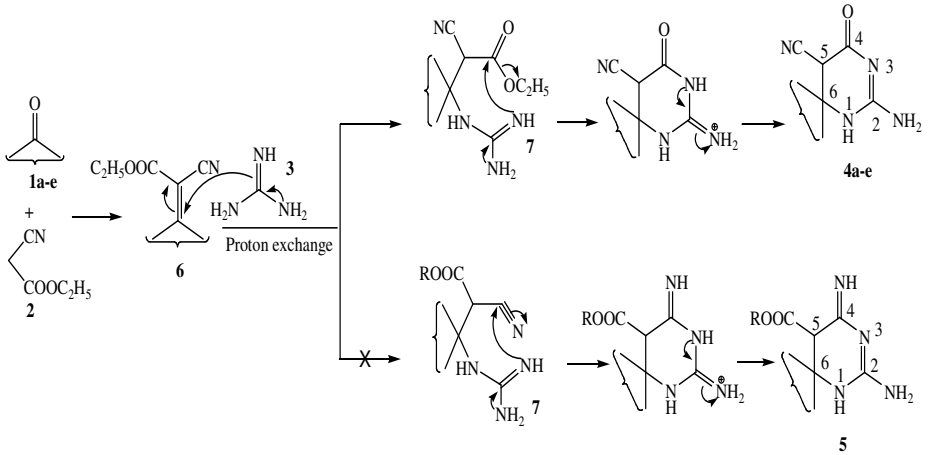
All the synthesized compounds were subjected to various physicochemical measurements. Molecular weights were determined by rast camphor method. Carbon and hydrogen analysis of the compounds done at the microanalytical laboratory, Department of Chemistry, Punjab University, Chandigarh. IR spectra were recorded on a Nicolet Megna FTIR-550 spectrophotometer using KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 NMR spectrometer at 300 MHz and 75 MHz respectively in DMSO-d_6 using trimethyl silane as internal standard. Mass spectrums of representative compounds were recorded on Kratos 50 mass spectrometer at 70eV. All the melting points were determined using open-ended capillary tube method.

*Regioselective synthesis of spiro-2-aminopyrimidine derivatives (**4a-e**)*

The synthesis of spiro-2-aminopyrimidine derivatives, In the ionic liquid procedure for the preparation of spiro derivatives, first step involves *in situ* formation of alkene derivative **(6)** by the knoevenagel condensation of cyclic ketone **(1a-e)** (1 mmol) and alkyl cyanoacetates **(2)** (1 mmol)**.** In the next step the formation of spiro derivatives **(4a-e)** was proceed via michael attack of free guanidine on **6** having electron attracting group on exomethylene carbon and afforded Micheal adduct **(7)**. The intermediate Michael adducts which has two possible nucleophilic groups (*i.e*. -CN and -COOR). This would lead to the formation of either spiro-2-aminopyrimidinones-5-carbonitrile **(4a-e)** or spiro-2-amino-4-imino-pyrimidin-5-carboxylic acid alkyl ester **(5)** subsequently. The reaction has been carried out in 25 mL ionic liquid [BMIM] [BF_4]. Reaction was completed in 2-3 h at 30-35 ^{o}C. The progress of the reaction was monitored by TLC (hexane: ethylacetate 10:1). After completion of reaction, the reaction mixture was cooled to 30 ^{o}C and then the reaction mixture was poured into ice-cold water, neutralized by 1:1 HCl solution to get the desired product. The separated solid was filtered by whatman filter paper under vacuum and washed with little amount of distilled water to remove acid. Desired product obtained as a solid with 82-87% yield, solid was crystallized by ethanol. Filtrate was completely distilled out at 80-85 ^{o}C under reduce pressure of 600 mm Hg to recycle ionic liquids which will be used for the synthesis of another compounds. The structures and reaction scheme of compounds **(4a-e)** are shown in Scheme 1 and 2.



Scheme 1. Regioselective synthesis of spiro-2-aminopyrimidine derivatives **(4a-e)**

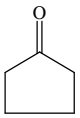
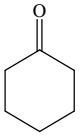
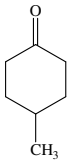
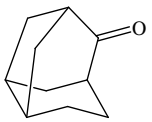
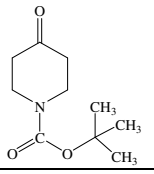


Scheme 2. Possible mechanisms of spiro-2-aminopyrimidine derivatives **(4a-e)**

Results and Discussion

The physical properties and analytical data of all the spiro-2-aminopyrimidine derivatives, are enlisted in Table 1. We have observed that the yield of compounds which contain electron withdrawing group is more than compounds having electron donating group. The time utilized for the synthesis of compounds using ionic liquid as a media is less as compared to commercial hazards solvents. Also the isolation of prepared compounds is more easy and eco-friendly in ionic liquid as compare to other hazards solvents. All the synthesized compounds are stable at ambient temperature, slightly soluble in ethanol, methanol and very soluble in DMF and DMSO.

Table 1. Analytical data and physical properties of the compounds synthesized by IL method

Compounds	Melting point, ^{0}C	Cyclic ketones	Found (Calculated) (%)			Melting point, ^{0}C
			C	H	N	
[BMIM] [BF_4] ($C_8H_{15}F_4N_2B$)	-	-	68.90 (69.02)	10.72 (10.86)	20.44 (20.12)	(139.22)
4a ($C_9H_{12}N_4O$)	282-284		56.40 (56.24)	6.31 (6.20)	29.24 (28.26)	(192.22)
4b ($C_{10}H_{14}N_4O$)	298-300		58.41 (60.20)	6.81 (6.74)	27.25 (27.79)	(206.24)
4c ($C_{11}H_{16}N_4O$)	310-312		59.79 (59.98)	7.34 (7.32)	25.52 (25.44)	(220.27)
4d ($C_{14}H_{18}N_4O$)	280-282		65.28 (65.09)	7.04 (7.02)	21.75 (21.69)	(258.32)
4e ($C_{14}H_{21}N_5O_3$)	260-262		54.54 (54.71)	6.86 (6.89)	22.72 (22.79)	(307.35)

Spectral data

*7-Amino-9-oxo-6,8-diaza-spiro [4.5] dec-7-ene-10-carbonitrile (**4a**)*

IR(KBr pellet, cm^{-1}):3325-3134 (NH & NH2), 2174 (C≡N), 1676 (C=O), 1585 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28-1.40 (m, 2H, CH2), 1.52-1.71 (m, 4H, CH2), 1.80-1.96 (m, 2H, CH2), 3.80 (s, 1H, CH), 6.86 (s, 2H, NH2, D2O exchangeable), 7.58 (s, 1H, NH, D2O exchangeable). ^{13}C NMR (100 MHz, $CDCl_3$):24.62 (C'1), 28.83 (C'4), 32.26 (C'3), 62.84 (C5-CN), 52.83 (spiro carbon), 115.48 (CN), 166.17 (C_2-NH_2), 182.62 (C=O),
MS: *m/z*: 193.56

*2-Amino-4-oxo-1,3-diaza-spiro [5.5] undec-2-ene-5-carbonitrile (**4b**)*

IR(KBr pellet, cm^{-1}):3320-3130 (NH & NH2), 2170 (C≡N), 1670 (C=O), 1590 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): 1.18-1.23 (m, 2H, CH2), 1.38-1.51 (m, 2H, CH2), 1.58-1.61 (m, 6H, CH2), 3.88 (s, 1H, CH), 6.92 (s, 2H, NH2, D2O exchangeable), 7.65 (s, 1H, NH, D2O exchangeable). ^{13}C NMR (100 MHz, $CDCl_3$): 20.4 (C'_1), 21.64 (C'_5), 24.8 (C'_4), 28.74 (C'_3), 34.29 (C'_2), 54.22 (spiro carbon), 61.87 (C_5-CN), 118.45 (CN), 170.11 (C_2-NH_2), 183.85 (C=O). MS: *m/z*: 207.77

*2-Amino-9-methyl-4-oxo-1,3-diaza-spiro [5.5] undec-2-ene-5-carbonitrile (**4c**)*

IR(KBr pellet, cm^{-1}):3324-3132 (NH & NH_2), 2174 (C≡N), 1668 (C=O), 1592 (C=N). ^1H NMR (400 MHz, $CDCl_3$): 1.22-1.28 (q, 3H, CH_3), 1.54-1.68 (m, 4H, CH_2), 1.74-1.84 (m, 4H, CH_2), 1.88-1.98 (m, 1H, CH), 3.90 (s, 1H, CH), 6.96 (s, 2H, NH_2, D_2O exchangeable), 7.68 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (100 MHz, $CDCl_3$):16.82 (CH_3), 26.46 (C'$_1$), 29.68 (C'$_5$), 34.87 (C'$_4$), 34.94 (C'$_2$), 38.25 (C'$_3$), 58.22 (spiro carbon), 64.54 (C_5-CN), 122.4 (CN), 176.12 (C_2-NH_2), 190.85 (C=O).
MS: *m/z*: 221.17.

*2-Amino-6-oxo-2,3,3a,4,5,5',6,6',7,7a-decahydro-1H,3H-spiro[2,5-methanoindene-8,4-pyrimidine]-5-carbonitrile (**4d**)*

IR(KBr pellet, cm^{-1}):3330-3138 (NH & NH_2), 2186 (C≡N), 1672 (C=O), 1592 (C=N). ^1H NMR (400 MHz, $CDCl_3$): 1.58-1.69 (m, 8H, CH_2), 1.72-1.88 (m, 5H, CH), 3.96 (s, 1H, CH), 6.98 (s, 2H, NH_2, D_2O exchangeable), 7.86 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (100 MHz, $CDCl_3$):24.4, 26.4, 27.4, 32.6, 38.8, 44.2, (aliphatic-C), 63.62 (C_5-CN), 60.28 (spiro carbon), 128.49 (CN), 180.94 (C_2-NH_2), 192.64 (C=O).
MS: *m/z*: 259.46.

*2-Amino-5-cyano-4-oxo-1,3,9-triaza-spiro [5.5]undec-2-ene-9-carboxylic acid tert-butyl ester (**4e**)*

IR(KBr pellet, cm^{-1}):3330-3140 (NH & NH_2), 2180 (C≡N), 1680-1700 two (C=O), 1598 (C=N). ^1H NMR (400 MHz, $CDCl_3$): 1.47 (s, 9H, C $(CH_3)_3$), 1.68-1.88 (m, 4H, CH_2), 2.08-2.32 (m, 2H, CH_2), 3.98 (s, 1H, CH), 6.96 (s, 2H, NH_2, D_2O exchangeable),7.78 (s, 1H, NH, D_2O exchangeable. ^{13}C NMR (100 MHz, $CDCl_3$):20.27 (CH_3), 24.95 (C $(CH_3)_3$), 28.75 (C'$_3$), 29.08 (C'$_5$), 37.08 (C'$_2$), 42.32 (C'$_6$), 54.43 (spiro carbon), 68.21 (C_5-CN), 118.64 (CN), 166.65 (C_2-NH_2), 172.61 (C=O), 180.24 (C_4=O).
MS: *m/z*: 308.67

Conclusion

An interesting regioselectivity is investigated in the multicomponent condensation of cyclic ketones, alkyl cyanoacetates and various guanidine salts using ionic liquids (3-butyl-1-methyl-1*H*-imidazol-3-ium tetrafluoroborate). Ionic liquid procedure resulted in the expected increment of yields, under ionic liquid the general applicability of this procedure is extended to a variety of ketones with high purity. Also addition of an ionic liquid increases the speed of reaction and reaction yields. It was possible to add catalytic quantities of ionic liquids in conventional solvent and still achieve a much greener reaction outcome. The prominent advantages of this methodology are reusability of the ionic liquids, operational simplicity, easy workup procedure, avoiding hazardous organic solvents and good yields of product.

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