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A Facile and Green Approach for the Synthesis of Spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile *via* One-Pot Three-Component Condensation Reaction using DBU as Catalyst

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Abstract

A series of functionalized spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile derivatives were synthesized using 1,3-dimethylbarbituric acid, aldehydes and cyclohexylidene malononitrile in presence of DBU. The structures were confirmed by spectral data. X-Ray crystallographic studies of one of the compounds confirmed the structure. The crystal packing shows eight molecules in a single unit cell. The crystal structure also revealed intermolecular and intramolecular hydrogen bonding. Mild reaction conditions, high yields, short reaction time and easy separation are some of the salient features of the present protocol.

Key words: 1,3-dimethyl barbituric acid, vinylogous Michael addition, Knoevenagel condensation, spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile, DBU.

Introduction

The development of novel methodologies for the synthesis of new diverse heterocycles with potential medicinal and biological activities compounds has become an important area of research in organic, combinatorial and medicinal chemistry.[1] Multicomponent reactions (MCRs), especially multicomponent domino reactions (MDR) are useful tools to achieve such aims.[2] The notable features of an MCR are construction of new bonds and functionalities during the cascade, which in turn, react further in subsequent steps under identical conditions until termination leads to a stable final product.[3] Therefore, the amount of solvents, reagents, energy and time in domino reactions are dramatically decreased compared to conventional stepwise approach and hence it plays an important role in organic synthesis.[4]

Spiro containing heterocycles are available in nature with interesting biological activities such as antimicrobial,[5] antimycobacterial,[6] antitumor,[7] antitubercular,[8] antimalarial,[9] and antioxidant.[10] One of the potential strategies for the synthesis and library production of these

spiro compounds is the application of multicomponent domino reactions. Pyrimidine core heterocycles are also show activities such as, bronchodilators,[11] vasodilators,[12] antiallergic,[13] antihypertensive,[14] anticancer[15] and antiHIV[16] (Fig. 1).

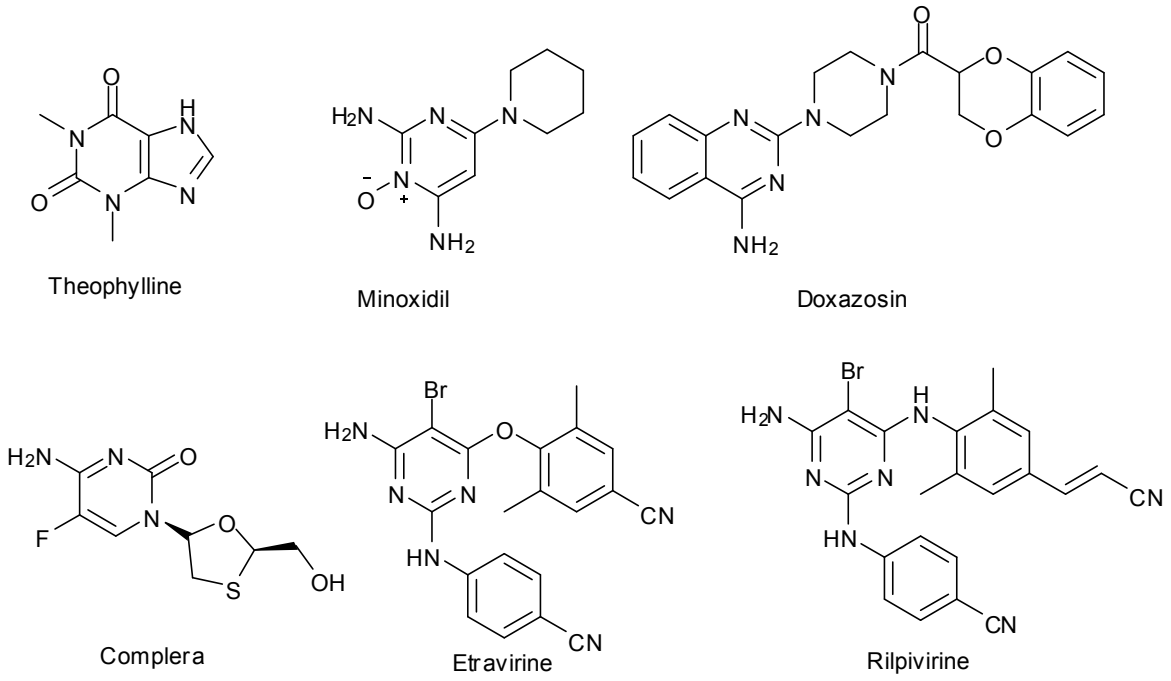


Figure 1: Pyrimidine core heterocycles containing drugs.

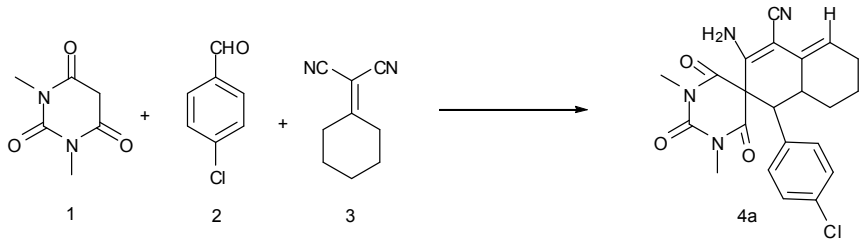
This encouraged us to design synthesis of novel spiro heterocycles having pyrimidine moiety. We conceived a synthesis starting from α,α-dicyanoalkenes[17] which can be synthesized by condensation of carbonyl compounds and malononitrile. α,α-Dicyanoalkenes are electron-deficient alkenes and inherently behave as electrophiles. The strong electron-withdrawing group activates the γ-position, and it undergoes the Michael addition[18] with α, β-unsaturated ketones. Moreover, vinylogous Michael addition reaction is important key step in the preparation of many spiro compounds.[19]

Therefore, in continuation of our research[20] for the synthesis of biologically active heterocyclic compounds with diverse applications through hybridization, we decided to investigate the synthesis of a novel class of spiro heterocycles from 1,3-dimethylbarbituric acid, aromatic aldehydes and α,α-dicyanoalkene by MCR domino approach.

Results and Discussion

This is the first report on the synthesis of highly functionalized spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile derivatives *via* one-pot three-component condensation of 1,3-dimethylbarbituric acid, aldehydes and cyclohexylidene malononitrile in ethanol using DBU (10 mol%) as catalyst at room temperature.

The optimization for the reaction was evolved after attempting model reactions of 1,3-dimethyl barbituric acid (1.0 mmol), 4-chlorobenzaldehyde (1.0 mmol) and cyclohexylidene malononitrile (1.0 mmol) in various solvents in presence of different catalysts. Initially, a reaction of the three reactants (1.0 mmol each) was carried out in EtOH in presence of $NaHCO_3$ (10 mol%) at room temperature. The reaction was found to be incomplete even after 6 h as monitored by TLC using ethyl acetate: petroleum ether (30:70, v/v) as eluent. The reaction mixture was quenched and the mixture separated by column chromatography. One of the products was identified to be the desired 3-amino-1-(4-chlorophenyl)-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile (4a) as characterized by spectral data (entry 1, Table 1) (Scheme 1). The yield of **4a**, however, was only 45%. The above reaction was then investigated with different catalysts namely, NaOH, NaOAc, Et_3N, piperidine, morpholine and DABCO (10 mol% each) under otherwise identical conditions. The reactions were not complete and gave desired **4a** after chromatographic separation with yields varying between 55-73% (entries 2-7, Table 1).



Scheme 1: Optimization reactions for the synthesis of 3-amino-1-(4-chlorophenyl)-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octa/decahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile (4a).

The same reaction was also explored using DBU (10 mol%) under identical conditions. The reaction was complete in 3 h and gave 89% of the desired product **4a** after work up (entry 8, Table 1). Reaction repeated using higher amount of DBU (20 mol%) did not affect the reaction rate or the yield of the product (entry 9, Table 1). Reaction carried out at 60 ^{o}C using 10 mol%

of DBU under otherwise identical condition was sluggish and yielded only 79% of **4a** after 3 h (entry 10, Table 1). Reaction using 10 mol% of DBU was also attempted in H_2O and DMSO. The reaction was incomplete after 9 h and yielded only 70 and 56% of **4a**, respectively (entries 11-12, Table 1). Reaction attempted in ethanol at room temperature in the absence of any catalyst gave only 13% of **4a** after 9 h (entry 13, Table 1). Therefore, the best optimum reaction condition for this one-pot three-component condensation reaction was using DBU (10 mol%) as catalyst in EtOH at ambient temperature. The results have been summarized in Table 1.

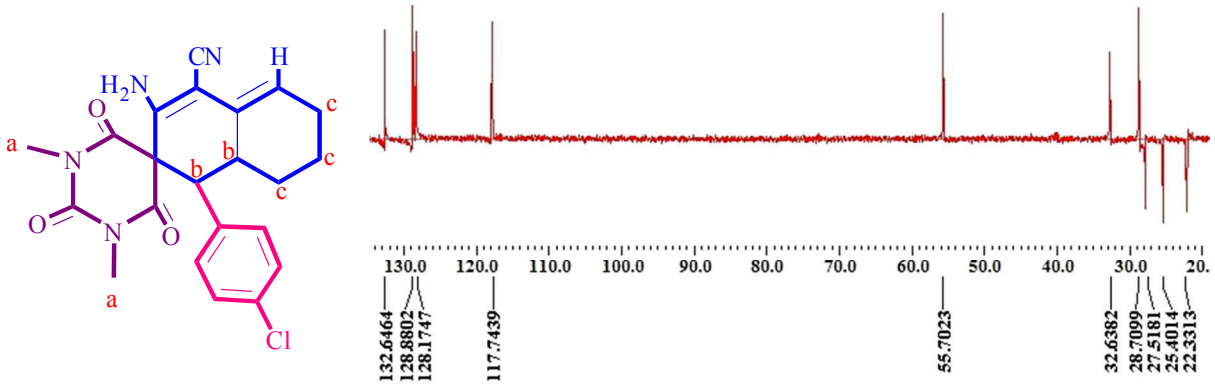
Table 1: Optimization reaction conditions for the synthesis of 3-amino-1-(4-chlorophenyl)-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile (4a).

Entry	Catalyst	Mol %	Solvent	Temp. (^oC)	Time (h)	Yield (%)[a]
1.	$NaHCO_3$	10	EtOH	RT	6	45
2.	NaOH	10	EtOH	RT	5	62
3.	NaOAc	10	EtOH	RT	5	66
4.	Et_3N	10	EtOH	RT	4.5	69
5.	Piperidine	10	EtOH	RT	4.5	71
6.	Morpholine	10	EtOH	RT	5	55
7.	DABCO	10	EtOH	RT	4	73
8.	DBU	10	EtOH	RT	3	89
9.	DBU	20	EtOH	RT	3	91
10.	DBU	10	EtOH	60	3	79
11.	DBU	10	H_2O	RT	9	70
12.	DBU	10	DMSO	RT	9	56
13.	-	-	EtOH	RT	9	13

[a] Isolated yield of **4a** after purifications.

The structure of **4a** was elucidated using NMR, IR and HRMS. The DEPT correlations were also useful in the signal assignment of **4a**. The mass spectrum of **4a** has a characteristic molecular ion peak (*m/z*) at 425.1362 $[M+H]^+$. The IR spectrum of compound **4a** shows strong absorption at 1669 cm^{-1} due to the carbonyl group. The weak absorption at 2201 cm^{-1} is due to the nitrile group. In ^1H NMR spectrum, a sharp singlet at 5.59 ppm corresponds to the vinylic

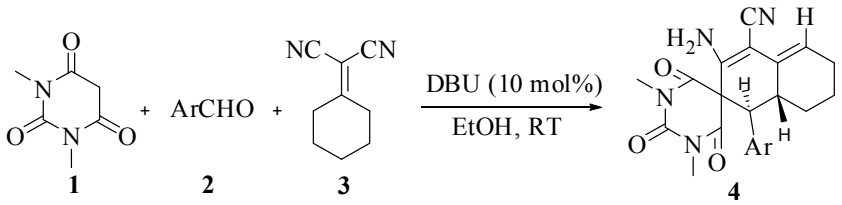
proton, one sharp singlet at 6.53 ppm is due to the –NH_2 protons. The methine proton appeared at 3.35 ppm. The doublet at δ 3.07 (1H, $^3J_{HH}$ = 12.8 Hz, CH) is due to benzylic proton. The coupling constant value of 12.8 Hz suggests the *trans* stereochemistry between the benzylic proton and methine proton which is also clearly observed from the single crystal X-ray analysis of compound **4a** (Fig. 3, Table 1) which further supports the ^{1}H NMR spectroscopy. The carbon signals at δ 128.8, 168.5 and 60.6 are due to carbon of nitrile, carbonyl carbon and spiro carbon, respectively (Figure 2). In DEPT, the stronger peak at 28.7 ppm comes from the pair of equivalent CH_3 carbons at position **a**. The vinylic carbon appeared at 117.7 ppm. The peaks at 55.7 ppm and 32.6 ppm are due to CH carbons at position **b** as it appears in both the DEPT-135 and DEPT-90 sub spectra. The inverse peaks at 27.5, 25.4 and 22.3 are due to CH_2 groups, and we can identify these as coming from the carbons at position **c**.



(a) (b)

Figure 2: (a) Representative compound **4a**. (b) DEPT-135 NMR spectrum of compund **4a**.

Subsequently, reactions of a variety of aldehydes were attempted with 1,3-dimethylbarbituric acid and cyclohexylidene malononitrile. All the reactions proceeded smoothly and were complete in 3 h to yield a diverse library of 3-amino-1-aryl-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitriles in high yields under the optimized protocol (Scheme 2). All the novel compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectra. All the results were summarized in Table 2.



Scheme 2: Synthesis of 3-amino-1-aryl-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

Table 2: Synthesis of 3-amino-1-aryl-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile[a]

Entry	Ar	Product No	Time (h)	Yield (%)[b]
1	4-ClC_6H_4	**4a**	3	89
2	4-FC_6H_4	**4b**	3	85
3	4-$(OCH_3)C_6H_4$	**4c**	2.5	92
4	4-$(CH_3)C_6H_4$	**4d**	2.5	90
5	4-$(NO_2)C_6H_4$	**4e**	3	91
6	4-$(CH_3)_2CHC_6H_4$	**4f**	2.5	88
7	3-BrC_6H_4	**4g**	3	82
8	2-$CH_3OC_6H_4$	**4h**	2.5	91
9	2-C_5H_3S	**4i**	3	87
10	4-$(CH_3)_2NC_6H_4$	**4j**	2.5	89
11	3-ClC_6H_4	**4k**	3	82
12	2- ClC_6H_4	**4l**	2.5	93
13	4-BrC_6H_4	**4m**	3	90
14	3-$(CF_3)C_6H_4$	**4n**	3.5	85
15	1-Naphtaldehyde	**4o**	2.5	88
16	Pyridine-2-carboxyaldehyde	**4p**	2.5	87
17	3,4,5-$(OCH_3)_3C_6H_2$	**4q**	2.5	92

[a]Reaction conditions: 1,3-dimethylbarbituric acid (1.0 mmol), aldehyde (1.0 mmol) and cyclohexylidene malononitrile (1.0 mmol) and DBU (10 mol%) in EtOH (5 mL) at RT.
[b]Yield of the product.

The structure of the synthesized novel 3-amino-1-(4-chlorophenyl)-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile

(4a) has also been confirmed by the single crystal X-ray diffraction analysis (Fig. 3). Single crystal of **4a** suitable for X-ray diffraction was obtained by layering method of CH_2Cl_2/hexane solutions at -4°C. The crystal packing shows eight molecules in a single unit cell (See supplementary data, Fig. 53a). Compound **4a** shows two chiral centres, with 'S' configuration at C7 position and 'R' at C8 position as observed from the crystal structure (Fig. 4). The crystal refinement data is listed in supplementary file (See in supplementary data Table 1).

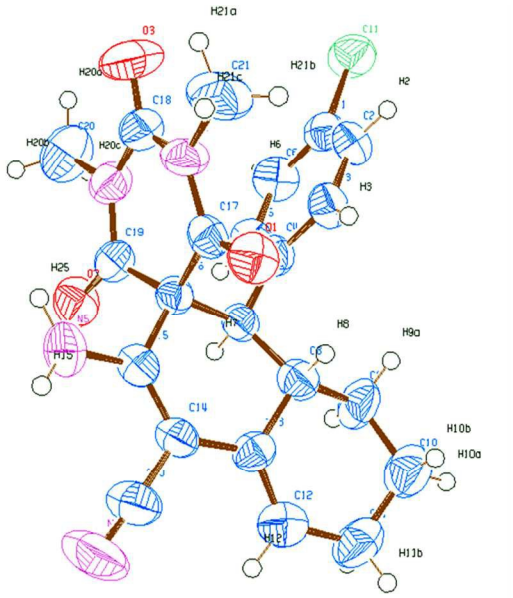
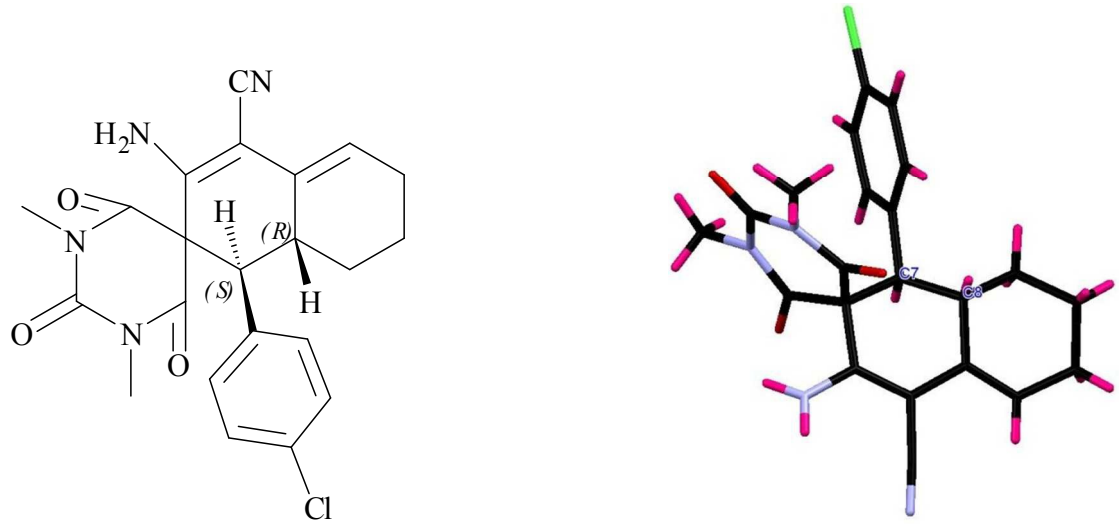


Figure 3: Ortep diagram of compound **4a** (CCDC-1420722).



(a) (b)

Figure 4: (a) Chemical structure of compound **4a** showing stereochemistry. (b) Perspective view of compound **4a**.

The compound **4a** revealed two types of interactions namely, intermolecular and intramolecular hydrogen bonding (See supplementary data, Table 2). The intermolecular H-bonding stabilized the molecule by bonding between N(5)-H(25)…N(3), N(5)-H(15)…O(3) and C(7)-H(7)…O(2) with a bond distance of 2.100, 2.552 and 2.311 Å, respectively (See supplementary data, Fig. 53b). The structure also involves intramolecular hydrogen bonding interactions between C(12)-H(12)…C(40), C(8)-H(8)…O(1), C(21)-H(21A)…O(3) with a bond distance of 2.498, 2.483 and 2.238 Å, respectively (Fig. 5).

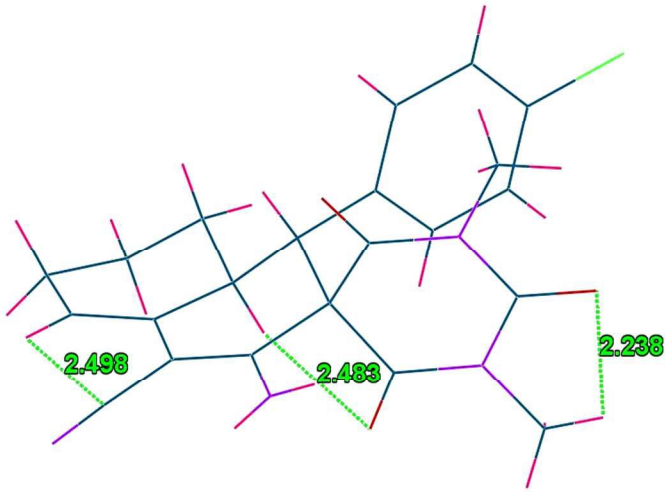
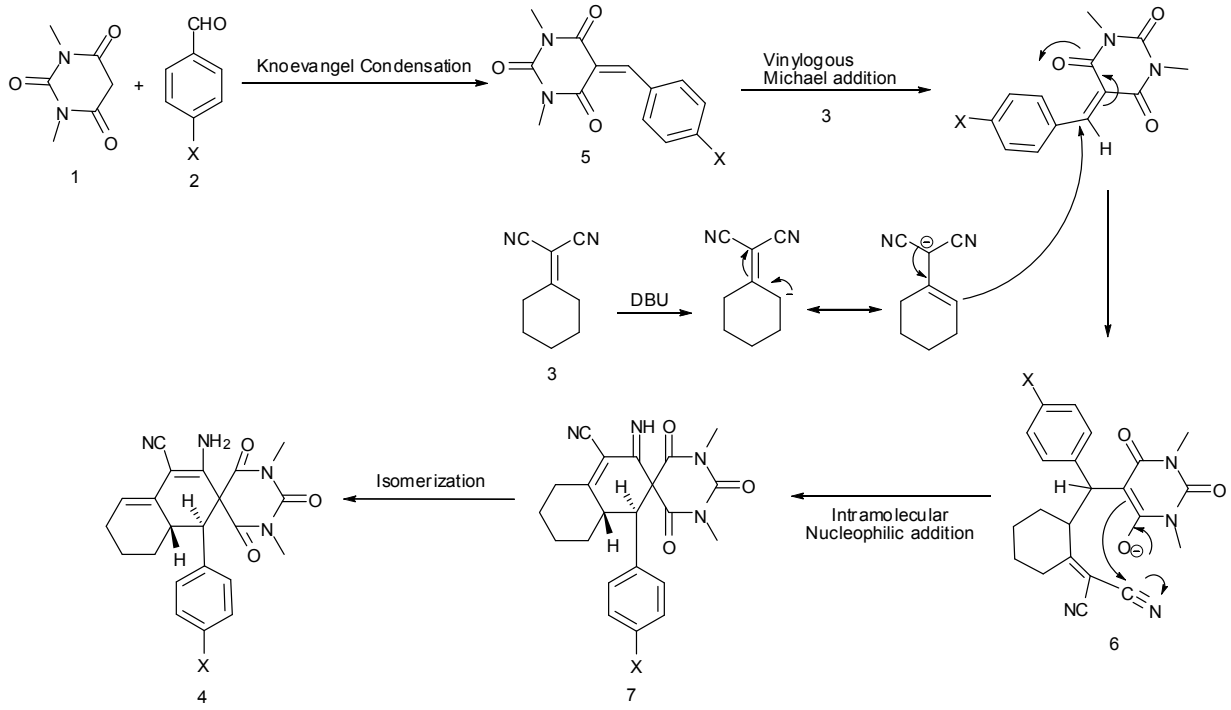


Figure 5: Intramolecular H-bonding of compound **4a**

A plausible reaction mechanism for the formation of spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile **4** is depicted in Scheme 3. Initially, 1,3-dimethylbarbituric acid (1) undergoes Knoevenagel condensation with aldehyde to yield Michael accepter **5**. The organic base removes γ-proton of cyclohexylidene malononitrile **3** to furnish cyclohexylidene malononitrile carbanion which undergoes Michael addition to enone **5** forming the intermediate **6.** The nucleophilic addition to the nitrile carbon from the least hindered side results the formation of intermediate **7** which upon isomerization[18b] gives the spirocarbocyclic compound **4**.



Scheme 3: Plausible reaction mechanism for the domino reaction.

Experimental

Silica gel 60 F_{254} Pre-coated Aluminium plates from Merck were used to monitor reaction progress. Melting points were determined on Buchi melting point 545 apparatus and are uncorrected. IR (KBr) spectra were recorded on a Perkin Elmer FTIR spectrophotometer, and the values are expressed as ν_{max}/cm^{-1}. The ^{1}H and ^{13}C spectra were recorded on Jeol JNM ECX-400P at 400 MHz and 100 MHz, respectively. Chemical shift values are recorded on δ scale, and the coupling constants (*J*) are in Hertz. Mass spectra were recorded at Bruker Micro TOF Q – II. The alkylidine malononitrile was prepared by reported procedure.[17]

Data Collection and Refinement

The intensity data for compound **4a** was collected on an Oxford Xcalibur CCD diffractometer equipped with graphite monochromatic MoK_{α} radiation (λ 0.71073 Å) at 293(2) K. The multi scan absorption correction was applied. The crystal structure of **4a** was solved by direct methods and refined by full-matrix least squares refinement techniques on *F*2 using *SHELXL-97*.[21] The coordinates of non-hydrogen atoms were refined anisotropically using *SHELXL-97*. The positions of hydrogen atoms were obtained from difference Fourier maps and were

included in the final cycles of refinement. All calculations were done using the *Wingx* software package.[21] Complete crystallographic data (excluding factors) of **4a** has been deposited at the Cambridge Crystallographic Data Centre under number CCDC 1420722.

General procedure for the synthesis of 3-amino-1-aryl-1',3'-dimethyl-2',4',6'-trioxo-2',3',4',6,6',7,8,8a-octahydro-1*H*,1'*H*-spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile (4a-4p)

An equimolar mixture of 1,3-dimethylbarbituric acid **1** (1.0 mmol), aldehyde **2** (1.0 mmol) and cyclohexylidene malononitrile **3** (1.0 mmol) was dissolved in 5 mL of EtOH in the presence of DBU (10 mol%) in a 50 mL round-bottomed flask. The reaction contents were stirred magnetically at room temperature (Table 2). The progress of the reaction was monitored by TLC (eluent: ethyl acetate: petroleum ether, 30:70, v/v). After completion of the reaction (Table 2), the reaction mixture was quenched with water (~5 mL). The precipitate formed was collected by filtration at pump and washed with water. The products were recrystalized by ethanol to give pure products (4a-4p). All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

Conclusion

In conclusion, we have developed a facile synthesis of spiro[naphthalene-2,5'-pyrimidine]-4-carbonitriles from 1,3-dimethylbarbituric acid (1), aldehydes (2) and cyclohexylidene malononitrile (3) in presence of DBU (10 mol%) in ethanol at room temperature. Mild reaction conditions, high yields, short reaction time and easy separation are some of the salient features of the present protocol. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass analysis.

Acknowledgement

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Supplementary Data

Supplementary data will be available for this article can be accessed on the publisher's website.

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Abstract

A series of functionalized spiro[naphthalene-2,5'-pyrimidine]-4-carbonitrile derivatives were synthesized using 1,3-dimethylbarbituric acid, aldehydes and cyclohexylidene malononitrile in presence of DBU. The structures were confirmed by spectral data. X-Ray crystallographic studies of one of the compounds confirmed the structure. The crystal packing shows eight molecules in a single unit cell. The crystal structure also revealed intermolecular and intramolecular hydrogen bonding. Mild reaction conditions, high yields, short reaction time and easy separation are some of the salient features of the present protocol.