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NBS/AIBN promoted one-pot multi component regioselective synthesis of spiro heterobicyclic rings via Biginelli-like condensation reaction

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ABSTRACT

N-Bromosuccinamide (NBS)/Azoisobutyronitrile (AIBN) efficiently catalyzed pseudo four-component reaction is described, leading to the efficient regioselective synthesis of σ symmetric spiro heterobicyclic rings using aldehydes and urea in the presence of cyclic β-diester or β-diamides such as Meldrum's acid or barbituric acid derivatives. The reaction proceeds in solvent-free conditions at 80^0 C.

Keywords: Biginelli Reaction, *N*-Bromosuccinamide, Multicomponent, Solvent-free, spiro heterobicyclic rings, Heterogeneous Catalysis.

INTRODUCTION

Multicomponent condensation reactions (MCRs) have recently been discovered to be a powerful method for the synthesis of organic compounds, since the products are formed in a single step and diversity can be achieved by simply varying each component [1-5].

The classic version of Biginelli [6] three-component condensation reactions, which combines an aldehyde, urea or thiourea and an open chain *β*-dicarbonyl compound under acidic conditions in ethanol to give 3,4-dihydropyrimidin-2-(1*H*)-ones, has entered into widespread use for generating large collections of molecules in combinatorial synthesis [7]. In recent years, there has been increasing interest in the design of new procedures for the synthesis of Biginelli and Biginelli-like compounds [8-11], which exhibit a wide range of biological activities, such as antiviral, antitumor, antihypertensive, α-1a-antagonist and neuropeptide Y(NPY) antagonist.

N-Bromosuccinimide (NBS), a mild source of bromine, is widely used in the presence of a catalytic amount of free-radical initiators for benzylic and allylic brominations with high regioselectivity [12]. In many instances, NBS has been used as an activator in stereoselective glycosidation [13], protection [14] and deprotection of ketals [15] or THP ethers [16] and in the synthesis of diindolylalkanes [17]. It is also widely employed as a mild oxidant [18] as well as for oxidative cyclizations [19, 20].

In continuation of our interest on the Biginelli reaction [21, 22], and the intention of extending the scope of the well-known multicomponent Biginelli reaction to the cyclic *β*-diesters or *β*-diamides, we have achieved the condensation of aldehydes and urea in the presence of Meldrum's acid or barbituric acid derivatives as a CH acid, instead of open

chain cyclic *β*-dicarbonyl compounds in the presence of *N*-Bromosuccinamide with catalytic amount of Azoisobutyronitrile as a radical initiator under solvent-free conditions at 80^0C.

EXPERIMENTAL SECTION

All the chemicals used were of AR grade purchased from Fluka, Merck and Aldrich Chemical Companies and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77MHz, respectively. NMR spectra were obtained using solutions in DMSO-d_6 with TMS as internal standard.

Synthesis of 3,3-dimethyl-(7S, 11R)-diphenyl-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5,9-trione under solvent-free conditions, typical procedure (4a):
An intimate mixture of benzaldehyde (0.30 g, 2 mmol), Meldrum's acid (0.144 g, 1 mmol), urea (0.06 g, 1 mmol), AIBN (1 mmol) and NBS (1.2 mmol) was placed in a screw-capped vial containing a magnetic stirring bar and was then heated at 80^0 C in a preheated oil bath for 4 h. After cooling NBS was separated by simple filtration due to its heterogeneous nature and the reaction mixture was poured onto crushed ice (40 g) and stirred for 5-10 min. The precipitate was filtered under suction, washed with cold water (40 mL) and ethyl acetate (5 mL) to afford the pure product **4a**. White powder. Mp 223-225^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3195 and 3060 (NH), 1771, 1731 and 1685 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 0.49 (6H, s, CMe_2), 5.29 (2H, s, 2CH), 7.20-7.37 (10H, m, Ar), 7.28 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 27.67 (C*Me*$_2$), 57.99 (C$_{spiro}$), 61.48 (2 CH), 105.51 (*C*Me$_2$), 127.72, 128.71, 129.26, and 135.54 (Ar), 155.22, 159.69, 165.55 (3C=O). MS (*m/z*, %) 380 (M$^+$, 11), 322 (7), 294 (13), 234 (12), 175 (17), 106 (100), 77 (44), 43 (56).

3,3-Dimethyl-(7S,11R)-bis(4-methylphenyl)-2,4-dioxa-8,10diazaspiro[5.5]undecane-1,5,9-trione **(4b):** White powder. Mp 199-200^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3200 and 3060 (NH), 1765, 1730 and 1686 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 0.51 (6H, s, CMe_2), 2.25 (6H, s, 2CH$_3$), 5.22 (2H, s, 2CH), 7.07-7.2 (8H, m, Ar), 7.17 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 20.62 (2CH$_3$), 27.73 (C*Me*$_2$), 57.99 (C$_{spiro}$), 61.21 (2CH), 105.44 (*C*Me$_2$), 127.56, 129.12, 132.52 and 138.66 (Ar), 155.31, 159.77, 165.64 (3C=O). MS (*m/z*, %) 408 (M$^+$, 14), 350 (7), 322 (11), 189 (27), 173 (36), 120 (100), 91 (69), 75 (14), 43 (59).

3,3-Dimethyl-(7S,11R)-bis(4-chlorophenyl)-2,4-dioxa-8,10diazaspiro[5.5]undecane-1,5,9-trione (4c): White powder. Mp 204-206^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3205 and 3065 (NH), 1770, 1731 and 1687 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 0.60 (6H, s, CMe_2), 5.32 (2H, s, 2CH), 7.21-7.47 (8H, m, Ar), 7.46 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 27.81 (C*Me*$_2$), 57.75 (C$_{spiro}$), 60.73 (2CH), 105.69 (*C*Me$_2$), 128.76, 129.62, 133.92 and 134.33 (Ar), 155.15, 159.63 and 165.32 (3C=O). MS (*m/z*, %) 449 (M$^+$, 16), 390 (7), 209 (22), 173 (36), 166 (57), 140 (98), 75 (14), 43 (100).

3,3-Dimethyl-(7S,11r)-bis(4-fluorophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5,9-trione (4d): White powder. Mp 216-218^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3205 and 3065 (NH), 1770, 1725 and 1680 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 0.59 (6H, s, CMe_2), 5.32 (2H, s, 2CH), 7.24-7.26 (8H, m, Ar), 7.47 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 27.80 (C*Me*$_2$), 58.03 (C$_{spiro}$), 60.69 (2CH), 105.62 (*C*Me$_2$), 115.65, 129.92, 131.64 and 155.27 (Ar), 159.79, 163.45 and 165.48 (3C=O). MS (*m/z*, %) 417 (M$^+$ +1, 136), 358 (12), 316 (9), 193 (26), 149 (68), 124 (90), 75 (34), 43 (100).

(7S,11R)-Diphenyl-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4e): White powder. Mp 240-242^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3240 and 3065 (NH), 1729 and 1695 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 5.21 (2H, s, 2CH), 7.17-7.31(10 H, m, Ar), 7.31 (2H, s, 2NH), 11.01 and 11.39 (2H, 2s, NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 57.49 (C$_{spiro}$), 61.59 (2CH), 127.81, 128.91, 129.36 and 136.12 (Ar), 149.11, 156.05, 165.88 and 170.31 (4C=O). MS (*m/z*,%) 364 (M$^+$, 5), 304 (10), 215 (95), 104 (100), 77 (96), 51 (98).

(7S,11R)-bis(4-Methylphenyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4f):
White powder. Mp 246-248^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3235 and 2975 (NH), 1724 and 1692 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 2.23 (6H, s, 2CH$_3$), 5.14 (2H, s, 2CH), 7.03-7.11 (8H, m, Ar), 7.01 (2H, s, 2NH), 10.97 and 11.33 (2H, 2s, NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 20.66 (2CH$_3$), 57.02 (C$_{spiro}$), 60.91 (2CH), 127.21, 128.98,

132.66 and 138.11 (Ar), 148.75, 155.66, 165.51 and 169.94 (C=O). MS (*m/z*, %) 364 (M^+ -CO, 7), 338 (25), 277 (31), 215 (100), 105 (87), 91 (23), 77 (39), 51 (45).

(7S,11R)-bis(4-Chlorophenyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4g):
Cream powder. Mp 291-293^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3146 and 3065 (NH), 1735 and 1708 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 5.21 (2H, s, 2CH), 7.15-7.41(8H, m, Ar), 7.20 (2H, s, 2NH), 11.14 and 11.51 (2H, 2s, NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 56.82 (C_{spiro}), 60.33 (2CH), 128.48, 129.23, 133.47 and 134.50 (Ar), 148.58, 155.42, 165.18 and 169.47 (C=O). MS (*m/z*, %) 432 (M^+- 1, 10), 400 (35), 372 (26), 249 (78), 215 (56), 138 (100), 75 (39), 51(69).

(7S,11R)-bis(4-Fluorophenyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4h):
White powder. Mp 213-215^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3195 and 3070 (NH), 1757, 1694 (C= O). ^{1}H NMR (DMSO, Me_4Si): δ_H 5.21 (2H, s, 2CH), 7.11-7.22 (8H, bs, Ar), 7.29 (2H, s, 2NH), 11.15 and 11.49 (2H, 2s, NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 57.05 (C_{spiro}), 60.28 (2CH), 115.27, 129.43, 131.73 and 150.19 (Ar), 155.47, 161.20, 165.35 and 169.62 (C=O). MS (*m/z*, %) 400 (M^+, 10), 350 (25), 233 (100), 190 (56), 122 (98), 95 (73), 75 (69), 51(69).

2,4-Dimethyl-(7S,11R)-diphenyl-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4i):
White powder. Mp 232-234^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3180 and 3060 (NH), 1739 and 1685 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 2.68 and 2.85 (6H, s, 2NMe), 5.28 (2H, s, 2CH), 7.08-7.28 (10 H, m, Ar), 7.18 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 27.87 and 28.71 (2NMe), 58.83 (C_{spiro}), 62.04 (2CH), 127.43, 128.84, 129.49, and 135.93 (Ar), 149.44, 155.87, 163.67 and 168.27 (4C=O). MS (*m/z*, %) 392 (M^+, 17), 260 (13), 243 (31), 186 (18), 106 (100), 77 (39), 51 (33).

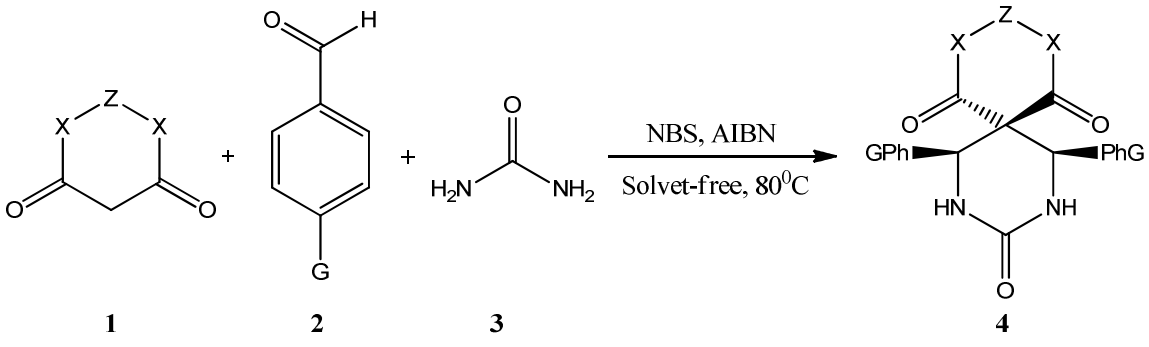
2,4-Dimethyl-(7S,11R)-bis(4-methylphenyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4j): White powder. Mp 228-230^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3195 and 3055 (NH), 1738 and 1686 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 2.21 (6H, s, $2CH_3$), 2.71 and 2.85 (6H, s, 2NMe), 5.22 (2 H, s, 2CH), 6.97-7.09 (8H, m, Ar), 7.08 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 20.64 ($2CH_3$), 27.42 and 28.72 (2NMe), 58.28 (C_{spiro}), 61.36 (2CH), 126.84, 128.86, 132.51, and 138.21 (Ar), 149.40, 155.35, 163.28 and 167.83 (4C=O). MS (*m/z*, %) 420 (M^+, 10), 360 (6), 274 (28), 257 (31), 186 (13), 120 (100), 106 (11), 91 (23), 77 (9).

2,4-Dimethyl-(7S,11R)-bis(4-chlorophenyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4k): White powder. Mp 271-273^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3195 and 3060 (NH), 1744 and 1659 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 2.74 and 2.87 (6H, s, 2NMe), 5.30 (2H, s, 2CH), 7.10-7.38 (8H, m, Ar), 7.25 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 27.53 and 28.34 (2NMe), 56.67 (C_{spiro}), 60.82 (2CH), 128.39, 128.97, 129.36, and 133.46 (Ar), 155.14, 156.72, 159.30 and 162.98 (4C=O). MS (*m/z*, %) 460 (M^+, 14), 400 (16), 321 (14), 294 (23), 277 (89), 220 (31), 140 (100), 75 (34).

2,4-Dimethyl-(7S,11R)-bis(4-fluorophenyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone (4l): White powder. Mp 244-246^{0}C dec. IR (KBr) (ν_{max}, cm^{-1}): 3190 and 3065 (NH), 1740, 1656 (C=O). ^{1}H NMR (DMSO, Me_4Si): δ_H 2.75 and 2.87 (6H, s, 2NMe), 5.30 (2H, s, 2CH), 7.13-7.15 (8H, m, Ar), 7.26 (2H, s, 2NH). ^{13}C NMR (DMSO, Me_4Si): δ_C 27.47 and 28.27 (2NMe), 58.28 (C_{spiro}), 60.76 (2CH), 115.21, 129.20, 131.60, and 148.93 (Ar), 155.24, 161.16, 163.12 and 167.53 (4C=O). MS (*m/z*, %) 428 (M^+, 10), 385 (6), 305 (17), 278 (33), 261 (69), 204 (31), 124 (100), 95 (35), 75 (34).

RESULTS AND DISCUSSION

As previously reported, the reaction of cyclic *β*-ketoesters [10] and *β*-diamides [11] Meldrum's acid or barbituric acid derivatives with 1 equivalent of urea and 2 equivalents of aldehydes gives a family of *σ* symmetric spiro heterobicyclic compounds in good yields in the presence of NBS/AIBN as a catalyst under solvent-free conditions at 80^0 C (Scheme 1).



1 **2** **3** **4**

X = O, Z = CMe_2
X = NH or NMe, Z = CO

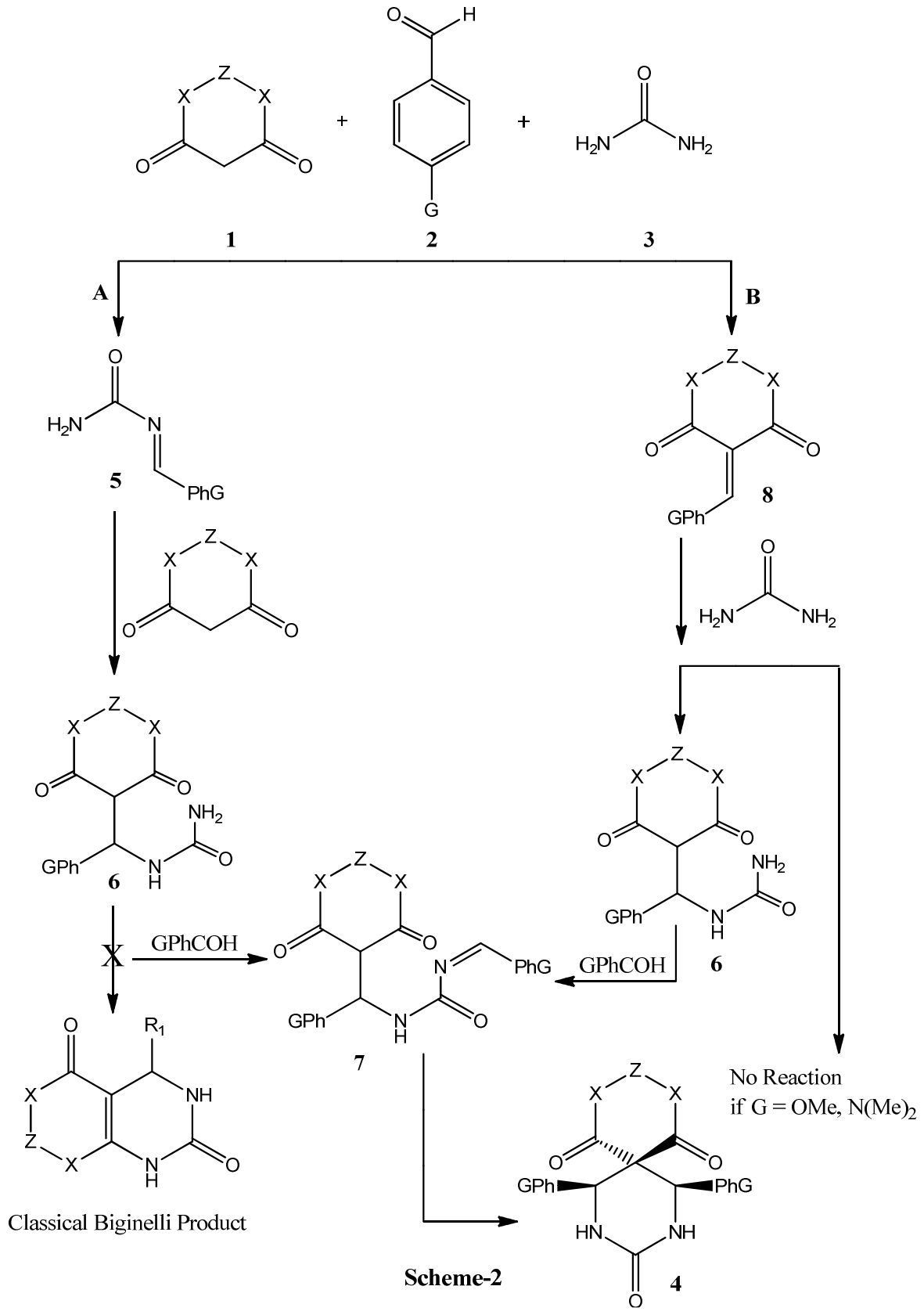
Scheme-1

The ^{1}H NMR spectrum of crude reaction mixture **4a** exhibited two single sharp lines readily recognized as arising from *CMe*$_2$ (δ_H 0.49) and two *CH* protons (δ_H 5.29). The phenylmoieties gave rise to multiplets in the aromatic region of the spectrum (δ_H 7.20-7.37). A broad singlet (δ_H 7.28) was observed for the two NH groups. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 11 distinct resonances in agreement with the σ symmetric structure. The σ symmetric stereoisomer is confirmed by the observation of three different signals for three carbonyl groups at δ 155.2, 159.7 and 165.5.

To explore the scope and limitations of this reaction further, we have extended it to various *para*-substituted benzaldehydes in the presence of Meldrum's acid and barbituric acid (Scheme 1). We have found that the reaction proceeds very efficiently with benzaldehyde and electron withdrawing *para*-substituted benzaldehydes, but it proceeded only up to Knoevenagel adducts, **8**, when electron releasing *para*-substituted benzaldehydes were used (X = OMe, NMe_2).

Table 1. Synthesis of spiro heterobicyclic rings 4(a-l) under solvent-free conditions at 80^{0}C

Entry	X-Z-X	G	Product	Yield (%)	M.P. (°C)
1	O-C(Me)$_2$-O	H	**4a**	76	223-225
2	O-C(Me)$_2$-O	Me	**4b**	74	199-200
3	O-C(Me)$_2$-O	Cl	**4c**	72	204-206
4	O-C(Me)$_2$-O	F	**4d**	73	216-218
5	HN-CO-NH	H	**4e**	93	240-242
6	HN-CO-NH	Me	**4f**	90	246-248
7	HN-CO-NH	Cl	**4g**	88	291-293
8	HN-CO-NH	F	**4h**	83	213-215
9	MeN-CO-NMe	H	**4i**	89	232-234
10	MeN-CO-NMe	Me	**4j**	91	228-230
11	MeN-CO-NMe	Cl	**4k**	83	271-273
12	MeN-CO-NMe	F	**4l**	82	244-246


1
2
3
A
B
5
8
6
6
GPhCOH
GPhCOH
7
No Reaction
if G = OMe, N(Me)2
Classical Biginelli Product
4

Scheme-2

We have not established a mechanism for the formation of spiro heterobicyclic compounds **4**, but two reasonable possibilities are indicated in Scheme 2. Addition of urea **3** to aldehyde **2** leads to highly reactive *N*-acylimine species **5** [23, 24] via a standard nucleophilic addition and dehydration reaction. Interception of **5** by Meldrum's acid or barbituric acid derivatives by a Michael-type addition reaction, possibly through its enol tautomer, produces an open chain ureide **6**, to which a second equivalent of aldehyde is added to furnish intermediate **7**. Subsequently, intermediate **7** cyclizes to the products **4** (Pathway A).

Aldehyde and cyclic *β*-diester or *β*-diamides would react via a standard Knoevenogel condensation reaction to produce compound **8** [24-27], followed by a Michael-type addition reaction with urea to afford ureides **6**, which react with another molecule of aldehyde and ultimately cyclize to the products **4** (Pathway B).

Since the reaction proceeds with electron releasing *para* substituted benzaldehydes only up to Knoevenagel adducts, the mechanism proposed in pathway B is expected to be slow. Differences in reactivity of variously substituted aldehydes could be rationalized if one supposes that the first or rate-limiting step is the nucleophilic attack of Meldrum's acid or barbituric acid on aldehydes, taking the route of a Knoevenagel condensation reaction (Pathway B in Scheme 2), or the nucleophilic reaction of urea with aldehydes as a first step of the classical Biginelli reaction [24] (Pathway A in Scheme 2). It is evident that electrondonating substituents not only decrease the reaction rate of the first step in both mechanisms A and B, but also that the Michael-type addition of urea to electron rich compounds **8** is stopped.

Recycling and Reusing of the Catalyst:

Reusability of the catalyst was also investigated. For this purpose, the model reaction for the synthesis of compound **4e** was studied under optimized reaction conditions. After the completion of the reaction, the catalyst was separated by simple filtration, washed with $CHCl_3$ (2x10 ml), EtOH (2x10 ml) and ether (2x10 ml) dried at 60^0 C under vacuum for 1 h, and reused for a similar reaction. As shown in Fig 1. the catalyst could be reused at least three times without significant loss of activity.

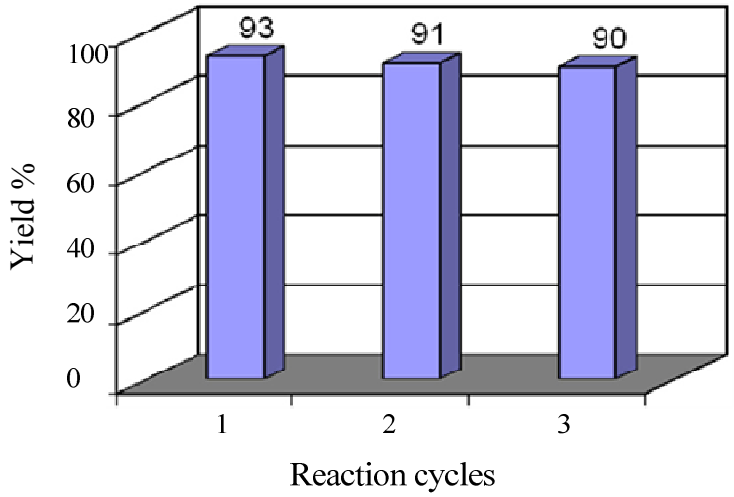


Fig 1. Reusability of NBS for model reaction.

CONCLUSION

In conclusion, we have reported a simple and new catalytic method for the synthesis of spiro heterobicyclic rings by one-pot four-component reaction of cyclic β-dicarbonyl compounds, aromatic aldehydes, and urea using NBS as an efficient, reusable, and green heterogeneous catalyst. The catalyst can be recycled after a simple work-up, and used at least three times without substantial reduction in its catalytic activity. High yields, and easy workup are few of the advantages of this procedure. We have also found that the reaction of strong C-H acids, such as Meldrum's acid or barbituric acid derivatives, with urea and aldehydes leads to a facile synthesis of planar symmetrical spiro heterobicyclic rings under solvent-free conditions at 80^0C.

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