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SHORT COMMUNICATION

Green chemistry approaches to the regioselective synthesis of spiro heterobicyclic rings using iodine as a new and efficient catalyst under solvent-free conditions

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Abstract Iodine catalyzes the pseudo four-component reaction of an aldehyde, a urea or thiourea, and cyclic 1,3-dicarbonyl compounds under microwave irradiation in a solvent-free condition to yield various σ symmetric spiro heterobicyclic rings in excellent yields.

Keywords Biginelli-like reaction · Barbituric acid · Spiro fused heterocycles · 1, 3-dicarbonyl compounds · Iodine · MCR · Multicomponent · Microwave synthesis

Introduction

In recent years, interest has been focused on Biginelli-like reactions [1] in which open chain β-dicarbonyl compounds have been extended to cyclic β-diketones [2], β-ketolactones [3], β-diamides [4–6], or cyclic β-diesters [4], benzocyclic ketones, and α-keto acids [7] under a variety of conditions, and the spiro heterocycles thus obtained exhibit a wide range of biological activities, such as antiviral, antitumor, antihypertensive, and neuropeptide Y(NPY) antagonism [4–6]. This is an impressive profile that bodes well for the interaction of this heterocyclic building block with a variety of biological targets of interests. However, the practical application of these methods suffers from disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, prolonged standing, and tedious manipulations in the isolation of the pure products.

Moreover, iodine is an electrophilic reagent that adds to alkenes and alkynes to give diiodides [8]. Alkenyl carboxylic acids react to give iodolactones and alkenylamides lead to iodolactams [9]. Iodine dehydrogenates amines and reacts with ketones in the presence of base to give α-iodo ketones [10]. Carboxylic acids are converted to α-iodo acid derivatives and carbanions react to give the substituted iodides [11], organoboranes can give alkyliodides [12], and vinyl boranes lead to substituted alkenes [13]. Iodine is also an important spotting reagent for TLC analysis. We hypothesized that the drawbacks of the catalysts employed in the Biginelli-like reaction may be avoided if we used iodine as a mild reagent. However, attention has so far been mainly paid to using open chained 1,3-dicarbonyl compounds to afford dihydropyrimidinone derivatives while the use of cyclic 1,3-dicarbonyl compounds has been seldomly reported (see Scheme 1)

Herein, we have developed a practical and general green chemistry approach for the Biginelli-type reactions using non-toxic and mild Lewis acid molecular iodine under microwave irradiation in solvent-free conditions. This method provides an efficient and much improved modification of a recently reported Biginelli-like scaffold in terms of higher yields, and catalyst role [14]. We employed microwave energy because the potential application of microwave technology in organic synthesis [15,16], particularly in solid state, is increasing rapidly due to its reaction simplicity, reduced polluting, and minimum reaction time providing rapid access to large libraries of diverse small molecules [17].

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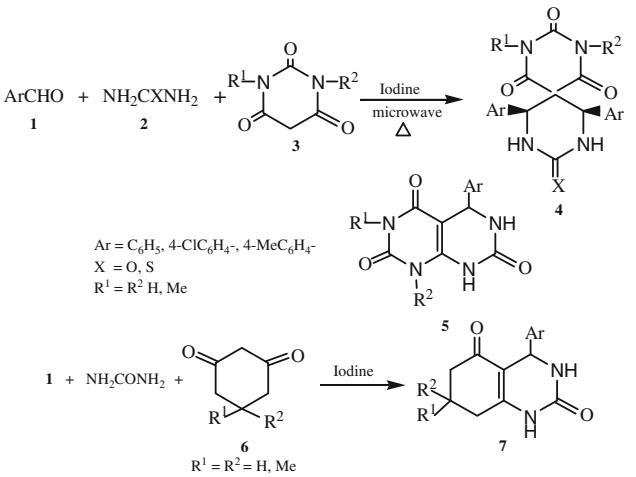


Scheme 1 Formation of spiro heterobicyclic compounds **4** and dehydropyrimidinones **7**

Experimental

General

Materials were obtained from commercial suppliers and were used without further purification. Melting points were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were recorded using KBr discs on a Perkin-Elmer 240C analyser. ^{1}H NMR spectra were recorded on a Varian EM-360L NMR spectrometer and the chemical shifts are reported in δ units (ppm) relative to Me_4Si as the internal standard. The 300 MHz NMR spectra were recorded using tetramethylsilane as internal standard (by RSIC, Shillong). Mass spectra were recorded on an AEIMS-30 spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. The microwave-assisted reactions were carried out in a Synthwave 402 Microwave reactor manufactured bv Prolabo [18]. All solvents were distilled before use. The progress of most reactions was monitored by TLC and flash chromatographic purification was performed with silica gel 60 (120 mesh, Merck).

Synthesis

Iodine-catalyzed Biginelli-type condensation under microwave irradiations: general procedure

In a typical procedure, a mixture of barbituric acid (1.30 g, 10 mmol), benzaldehyde (3.20 g, 30 mmol), urea (0.6 g, 10 mmol), and iodine (0.01 g, 0.1 mmol) was placed in a reaction vessel and irradiated in a Prolabo Synthwave Microwave Reactor for 4 min. After completion, (monitored by TLC) the reaction mixture was cooled to room temperature and poured onto ice-cold water (30 mL). The resulting solid was filtered, washed with water, and then recrystallized from ethanol to afford pure spiro-(2-oxo-4,6-diphenylhexahydropyrimidine-5,5′-barbituric acid) **4a**, Mp 240−241° C (lit. Mp 241 − 242° C [14]) in 94% yield. Similarly other substituted aldehydes, barbituric acids or substituted barbituric acids, and urea or thiourea were reacted together to produce the corresponding spiroheterocycles **4b-j** in high yields. The results are summarized in the Table 1.

Spiro-(2-oxo-4,6-diphenylhexahydropyrimidine-5,5′-barbituric acid): **4a**

Mp 240 − 241° C (d). IR (KBr), 3360, 3150 (NH), 1735 and 1690 (CO) cm^{-1}. ^{1}H NMR (400 MHz, DMSO − d_6) : δ_H, 5.30 (s, 2H, 2CH), 7.10–7.50 (m, 10H, aromatic), 7.65 (s, 2H, NH), 11.02, 11.36 (2s, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) : δ c 57.5 (C-spiro), 62.2 (2CH), 127.8, 129.0, 129.5, 137.1, 150.1, 156.1, 166.5, and 170.5 (4CO). Anal. Calcd for $C_{19}H_{16}N_4O_4$: C, 62.64; H, 4.40; N, 15.38. Found: C, 62.73; H, 4.49; N, 15.33.

Spiro-[2-oxo-4,6-diphenylhexahydropyrimidine-5,5′-(1′-methylbarbituric acid)]: **4d**

Mp 234 − 236° C (d). IR (KBr), 3195, 3300 (NH), 1730 and 1688 (CO) cm^{-1}. ^{1}H NMR: δ_H, 2.70 (3H, s, NMe), 5.35 (2H, s, 2CH), 7.08–7.35 (10H, m, aromatic), 8.80 (2H, s, NH). ^{13}C NMR: δ c 28.8, 56.5, 62.8, 126.8, 128.8, 130.2, 136.2, 150.6, 154.8, 167.2, and 171.1. Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.49; H, 4.76; N, 14.81. Found: C, 63.40; H, 4.83; N, 14.76. Similarly dimedone and cyclohexane 1,3-dicarbonyl compounds were reacted with urea and aldehydes in presence of iodine under microwave irradiation and the corresponding 3,4-dihydropyrimidinones **7** were obtainded in 85–96% yields.

7a: Mp 226 − 230° C (d) IR (KBr), 3330, 2960, 1705, 1640, and 1380 cm^{-1}. ^{1}H NMR: δ_H 0.72–1.12 (6H, s, $2CH_3$), 1.95–2.25 (4H, d, $2CH_2$), 5.10 (1H, s, CH), 6.90–7.42 (5H, m, ArH), 8.55 (1H, s, NH), 8.75 (1H, s, NH); ^{13}C NMR: δ c 25.8, 27.4, 33.6, 40.8, 49.6, 53.2, 107.8, 127.8, 129.0, 129.5, 140.5, 151.8, 155.8, and 193.8.

7b: Mp 238 − 242° C (d) IR (KBr), 3250, 3090, 2960, 1705, 1655, 1610, and 1470 cm^{-1}. ^{1} H NMR: δ_H, 0.84–1.22 (6H, s, $2CH_3$), 2.02–2.28 (4H, d, $2CH_2$), 5.15 (1H, s, CH), 7.04–7.52 (4H, m, ArH), 8.60 (1H, s, NH), 8.82 (1H, s, NH); ^{13}C NMR: δ c 26.4, 28.2, 32.8, 39.6, 50.4, 51.8, 106.5, 127.8, 129.0, 130.6, 132.4, 146.2, 150.1, 155.8, 192.8.

7c: Mp > 290° C, IR (KBr), 3280, 3260, 3065, 2970, 1710, and 1680 (CO) cm^{-1}. ^{1}H NMR: δ_H, 1.92–2.36 (6H, m, CH_2), 5.25 (1H, s, CH), 7.54 (2H, m, ArH), 7.76 (3H, m, ArH), 8.65 (1H, s, NH), 8.84 (1H, s, NH). ^{13}C NMR: δ c 32.4, 39.6, 48.8, 52.8, 106.6, 127.8, 129.0, 129.5, 130.8, 132.8, 146.2, 150.1, 155.8, 166.5.

Table 1 Iodine catalysed synthesis of spiro heterobicyclic compounds **4** and dehydropyrimidinones **7**

Entry	Products[a]	Ar	R^1	R^2	X	Reaction time microwave (min)	Yields[b] (%) microwave	Mp (°C)	Lit. M.p. (°C)
1	**4a**	Ph	H	H	O	4.5	94	240–241	241–242 [12]
2	**4b**	4-ClC_6H_4	H	H	O	4.0	95	289–291	289–291 [12]
3	**4c**	4-MeC_6H_4	H	H	O	4.5	93	245–248	246–248 [12]
4	**4d**	Ph	H	CH_3	O	4.0	95	234–236	–
5	**4e**	4-ClC_6H_4	H	CH_3	O	4.5	92	269–272	–
6	**4f**	4-MeC_6H_4	H	CH_3	O	4.5	90	266–268	–
7	**4g**	Ph	CH_3	CH_3	O	4.0	95	231–232	231–232 [12]
8	**4h**	4-ClC_6H_4	CH_3	CH_3	O	4.0	96	270–273	271–273 [12]
9	**4i**	4-MeC_6H_4	CH_3	CH_3	O	4.5	94	226–228	227–229 [12]
10	**4j**	Ph	H	H	S	4.5	50	245–247	245–247 [12]
11	**4k**	Ph	CH_3	CH_3	S	4.5	52	242–244	242–244 [12]
12	**7a**	Ph	CH_3	CH_3	O	1.5	95	226–230 (d)	–
13	**7b**	4-ClC_6H_4	CH_3	CH_3	O	1.5	96	238–240(d)–	
14	**7c**	Ph	H	H	O	1.5	86	>290(d)	–

[a] All the compounds were characterized by IR, NMR, MS, and Mp
[b] Isolated yields

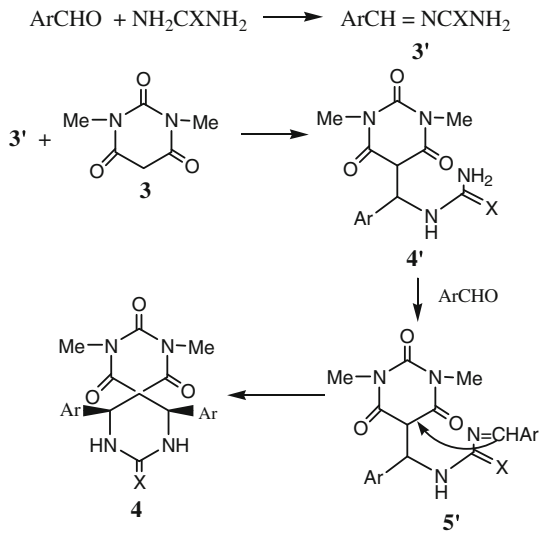
Biginelli-type reaction catalyzed by iodine under thermolytic conditions: general procedure

The reaction was carried out similarly by heating the reaction mixture in the solid state at 60 °C in an oil bath and on completion and after usual work-up the corresponding spiro heterocycles **4** were obtained in 75–85% yields.

Results and discussion

We performed a pseudo four-component Biginelli-type reaction using barbituric acid derivatives in place of the usually used open chain β-dicarbonyl compounds. The reaction was carried out by heating a mixture of barbituric acid, urea, and an aldehyde in presence of 1 mol% iodine under microwave irradiation for 4.0–4.5 min. After work-up the corresponding spiropyrimidine barbituric acid derivative **4a** was exclusively obtained in 94% yield without the formation of classic Biginelli-derived product **5**.

Treatment of 1 equiv each of barbituric acid, urea and aldehyde under microwave irradiation in presence of iodine did not produce the desired spiropyrimidine derivative **4** in good yields. However, the reaction proceeds efficiently, without the formation of any side products when 2 equiv of aldehyde and 1 equiv of urea and barbituric acid were employed. During our investigation, it was observed that 1 mol% of iodine is sufficient to perform the reaction as the conversion decreased when a smaller amount of iodine was used. When the same reaction is carried out under thermal heating at 60 °C the corresponding spiro heterobicyclic products **4a–i** are obtained in 75–85% yields. The structure of all the symmetrical spiroheterocyclic compounds obtained were confirmed by spectral analyses and by comparison against an authentic sample. From spectroscopic studies it is observed that the reaction is driven by a regiospecific condensation of two moles of aldehyde with one mole of urea and one mole of barbituric acid to afford exclusively the *cis* configuration of the spiro pyrimidine barbituric acid. In the case where thiourea was used under similar microwave irradiation conditions only spiro[2-thioxo-4,6-diphenyl hexahydropyrimidine-5,5′-(barbituric acid)] **4j** was obtained (50% yield). Longer reaction times (e.g., 10 min) did not improve yields, and resulted in decomposition of starting material. Remarkably, when the same reaction was carried out without microwave energy in the solid state at 60 °C, the corresponding spiro heterocyclic ring **4j** was obtained in 81% yields. To explore the synthetic scope of this Biginelli-like reaction further, various *para*-substituted benzaldehydes, urea or thiourea, *N*-substituted or unsubstituted barbituric acids were employed under microwave irradiation. Contrary to earlier reports [14], with our system this reaction proceeds efficiently with electron-releasing or electron-withdrawing *para*-substituted benzaldehydes (90–96% yields). Notably, when we employed cyclic 1,3-dicarbonyl compounds such as dimedone or cyclohexane-1,3-dione **6** in the above reaction, under identical condition we did not observe the formation of any spiro heterobicyclic rings, rather we got the corresponding dihydropyrimidinones **7** [7] as observed by Abelman et al. with α and β-tetralones.



Scheme 2 Mechanism for the formation of spiro heterobicyclic compounds **4**

Although the mechanism of this reaction has not been experimentally elucidated, it is likely that *N*-acylimine species **3′** is formed first by the reaction of urea and aldehyde *via* a nucleophilic addition and dehydration [19,20]. Subsequent addition of the iminium ion to barbituric acid derivatives in presence of iodine catalyst produces an open chain ureide **4′**. The second molecule of aldehyde is then added to the ureide **4′** to furnish intermediate **5′**, which subsequently cyclizes to provide spiro heterobicyclic ring **4** (Scheme 2). Alternatively, aldehyde and barbituric acid may react via a Knoevenagel condensation reaction [20,21], followed by a Michael type reaction with urea to produce ureide **4′**. This then reacts with a second molecule of aldehyde, which ultimately cyclizes to the desired product. Further work is in progess to understand the exact mechanism of the reaction.

Conclusion

In conclusion, the present method discloses a new and simple method for the synthesis of various symmetrical spiro heterobicyclic compounds using molecular iodine in excellent yields under microwave irradiations. This iodine-catalyzed one-pot synthesis is simple, high yielding, time saving, and environment friendly. In addition to its simplicity and selectivity this reaction has one salient feature in its ability to tolerate a variety of aldehydes and constitutes a useful alternative to the commonly accepted procedures.

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References

1. Biginelli P (1893) Synthesis of tetrahydropyrimidinones by the acid catalyzed condensation of an aldehyde, a β-ketoester and urea. Gazz Chim Ital 23:360–416
2. Yarim M, Sarac S, Kilic FS, Erol K (2003) Synthesis and in vitro calcium antagonist activity of 4-aryl-7,7-dimethyls1,7, 7,-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives. Il Farmaco 58:17–24. doi:10.1016/S0014-827X(02)00009-5
3. Byk G, Gettlieb HE, Herscovici J, Mirkin F (2000) New regioselective multicomponent reaction: One pot synthesis of spiro heterocyclic aliphatic rings. J Comb Chem 2:732–735. doi:10.1021/cc000056p
4. Mokrosz JL, Paluchowska MH, Szneler E, Drozdz B (1989) The effect of aryl substituents in some spiro[2-oxo-4,6-bis(aryl)hexahydropyrimidine-5,5′-barbituric acids]. Arch Chem (Weinheim, Germany) 322:231–235
5. Mamaev VP, Borovik VP (1968) Spiro[2-oxo-4,6-bis(aryl)hexahydropyrimidine-5,5′-barbituric acids]. Izobret Prom Obraztsy Tovarnye Znaki 45:24; Chem Absrt 69: 96790f
6. Borovik VP, Mamaev VP (1970) Synthesis of sulfur-containing spiropyrimidine barbituric acids. Kim Farm Zh 4:32–35; Chem Abstr 72:111411
7. Abelman MM, Smith SC, James DR (2003) Cyclic ketones and substituted α-keto acids as alternative substrates for novel Biginelli-like scaffold synthesis. Tetrahedron Lett 44:4559–4562. doi:10.1016/S0040-4039(03)00985-7
8. Field KW, Wilder D, Utz A, Kolb KE (1987) Addition of Iodine to alkenes: A pseudo first-, second-, or third- order kinetics experiment. J Chem Educ 64:269–270. doi:10.1021/ed064p269
9. Klein J (1959) The Iodolactonization of Cyclohexaneacetic Acids. J Am Chem Soc 81:3611–3614. doi:10.1021/ja01523a035
10. Freiberg LA (1967) Mechanism of oxidation of enolizable nonmethyl ketones by base and iodine. The role of atmospheric oxygen. J Am Chem Soc 89:5297–5298. doi:10.1021ja00996a045
11. Kirk KC (1978) Facile synthesis of 2-substituted imidazoles. J Org Chem 43:4381–4383. doi:10.1021jo00416a033
12. Brown HC, Rathke MW, Rogic MM, DeLue NR (1988) Organoboranes for synthesis. 9. Rapid reaction of organoboranes with iodine under the influence of base. A convenient procedure for the conversion of alkenes into iodides via hydroboration. Tetrahedron 44:2751–2762. doi:10.1016/S0040-4020(88)90010-5
13. Zweifel G, Fisher RP, Snow JT, Whitney CC (1972) Convenient synthesis of trans olefins from alkynes via hydroboration-cyanohalogenation. J Am Chem Soc 94:6560–6561. doi:10.1021/ja00773a059
14. Shaabani A, Bazagir A (2004) Microwave-assisted efficient synthesis of spiro-fused heterocycles under solvent-free conditions. Tetrahedron Lett 45:2575–2577. doi:j.tetlet.2004.01.154
15. Santagada V, Frecentese F, Perissutti E, Favretto L, Caliendo G (2004) The application of microwaves in combinatorial and high-throughput synthesis as new synthetic procedure in drug discovery. QSAR Comb Sci 23:919–944. doi:10.1002/qsar.200420039
16. Choudhary VR, Tillu VH, Narkhede VS, Borate HB, Wakhardar RD (2003) Microwave assisted solvent-free synthesis of dihydropyrimidinones by Biginelli reaction over Si-MCM-41 supported FeCl3 catalyst. Cat Commun 4:449–453. doi:10.1016/S1566-7367(03)/00111-0
17. Kuhnert N (2002) Microwave-assisted reactions in organic synthesis—Are there any nonthermal microwave effects?. Angew Chem Int Edn 41:1863–1866. doi:10.1002/1521-3773(20020603)41:11<1863

18. Manufactured by M/s Prolabo, 54 rue Roger Salengro; F-94126 Fontenay-Sous-Bois, Cedix- France, Tel: 01 45 14 85 00; Fax: 01 45 14 85 15; Fax Export: 33 145148616
19. Kappe CO (1997) A reexamination of the mechanism of the Biginelli dihydropyrimidine synthesis. Support for an N-acyliminium ion intermediate. J Org Chem 62:7201–7204. doi:10.1021/jo971010u
20. Folkers K, Johnson TB (1933) Researches on pyrimidines. CXXXVI. The mechanism of formation of tetrahydropyrimidines by the Biginelli reaction. J Am Chem Soc 55:3784–3791. doi:10.1021/ja01336a053
21. Kaup G, Reza Naim MJ, Schmeyers J (2003) Sovent free Knoevenagel condensation and Michael additions in the solid state and in the melt with quantitative yield. Tetrahedron 59:3753–3760. doi:10.1016/S0040-4020(03)00554-4