Molecular iodine-catalysed tandem synthesis of oxospirotricyclic furopyrimidines in water

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A simple, efficient and high yielding one-pot protocol for the synthesis of oxospirotricyclic furobarbiturates was developed by pseudo three-component domino coupling of barbituric acids and various benzaldehydes in water, catalysed by molecular iodine.

Keywords: barbituric acids, benzaldehydes, iodine, spiro compounds

Nowadays organic chemists are required to investigate clean, economical and environmentally safer methodologies.[1] The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.[2] One of the fundamental challenges and ultimate goals for reactions of organic molecules is to perform the reaction in water,[3] because the application of water would reduce the use of harmful organic solvents and lead to the development of environmentally friendly processes.

Molecular iodine has gained importance as an inexpensive, non-toxic and readily available catalyst for various organic transformations affording the corresponding products with high selectivity in excellent yields (see reference[4] and references cited therein). The mild Lewis acidity associated with iodine enhances its use in organic synthesis to perform several organic transformations using stoichiometric or catalytic amounts.

Compounds containing a fused pyrimidine ring represent a broad class of compounds which have received considerable attention due to their wide range of biological activities.[5] A survey of the literature revealed that furopyrimidines have been the object of intense investigation in organic synthesis and medicinal chemistry and several approaches have been reported for the synthesis of these heterocyclic compounds.[6–8] In 2010, Elinson *et al*. reported the first synthesis of spiro-derivatives of {furo[2,3-*d*]pyrimidine-6,5'-pyrimidine}pentone *via* a cascade assembly of 1,3-dialkylbarbituric acids and benzaldehydes in the presence of molecular bromine.[7] Later, they examined the electrocatalytic transformation of benzylidenebarbituric acids and 1,3-dialkylbarbituric acids into spirobarbiturates containing the furo[2,3-*d*]pyrimidine framework.[8] It should be noted that although synthesis of {furo[2,3-*d*]pyrimidine-6,5'-pyrimidine}pentones has been reported in the literature,[7,8] no attempts were made to utilise 2-thiobarbituric acid derivatives and also unsubstituted barbituric acid to furnish thio-analogues of the products. Notably, one of the drawbacks of the previously described method for the synthesis of {furo[2,3-*d*]pyrimidine-6,5'-pyrimidine}pentones was the use of molecular bromine as a volatile, hazardous and strongly corrosive oxidant. Recently we have reported that the urotropine-bromine complex is a safe source of active bromine and promotes the reaction between barbituric acids and benzaldehydes yielding oxospirotricyclic furobarbiturates.[9] To expand and improve this type of domino process, we have now utilised thio-analogues of barbituric acid and unsubstituted barbituric acid and also molecular iodine as a mild oxidant in water to produce spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine} derivatives.

In continuation of our efforts to develop one-pot protocols[10–13] for the synthesis of biologically important heterocycles in water, we describe here a straightforward one-pot synthesis of 5-aryl-1,5-dihydro-2*H*,2'*H*-spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine} derivatives promoted by molecular iodine in aqueous media, as an improved and expanded paper that includes more results compared to another report.[7] Our literature survey at this stage revealed that there is no report yet available on the synthesis of spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine} derivatives in one-pot procedures by pseudo three-component coupling of aromatic aldehydes and barbituric acids in water promoted by iodine. In fact, as clearly stated by Sheldon, it is generally recognised that "the best solvent is no solvent and when a solvent (diluent) is needed then water is the preferred choice".[14]

Initially, the pseudo three-component coupling reaction of barbituric acid (**1a**) and benzaldehyde (**2a**) in water was examined without any catalyst at room temperature. It was found that no desired product **3a** was observed by TLC analysis even after 24 h, while undesired products of Knoevenagel condensation and also Michael addition adducts were formed under the above conditions. Subsequently, the addition of molecular iodine to the above reaction mixture resulted in the desired product **3a** in good yield.

Encouraged by these results obtained with the above reaction conditions and in order to show the generality and scope of this new protocol, we used eleven variously substituted benzaldehydes and four barbituric acid derivatives (Scheme 1). Four derivatives of barbituric acids (barbituric acid, 1,3-dimethylbarbituric acid, 2-thiobarbituric acid and 1,3-diethyl-2-thiobarbituric acid) afforded oxospirotricyclic furobarbiturates in good to excellent isolated yields. Also, the results showed that substituted benzaldehydes containing electron-withdrawing groups (*o*-, *m*- and *p*-NO_2, *p*-CN, *o*-, *m*- and *p*-Cl and *p*-Br and *p*-F) and electron-donating groups at the *meta* position (*m*-OH) all tolerate the reaction conditions with excellent yields.

Scheme 1 clearly demonstrates that molecular iodine is an excellent catalyst for this one-pot three-component reaction in water. Notably, the reactions were clean and all the products were easily isolated simply by filtration and washing with water.

A probable mechanistic rationale portraying the sequence of events for this domino coupling is postulated in Scheme 2. The first step is believed to be the Knoevenagel condensation between a barbituric acid **1** and an aldehyde **2** to generate adduct **4**, which acts as a Michael acceptor. The second barbituric acid molecule **1** attacks adduct **4** in a Michael-

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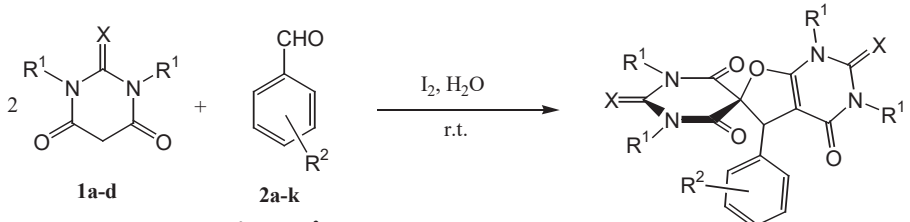


1a-d

a R^1 = H, X = O
b R^1 = H, X = S
c R^1 = Me, X = O
d R^1 = Et, X = S

2a-k

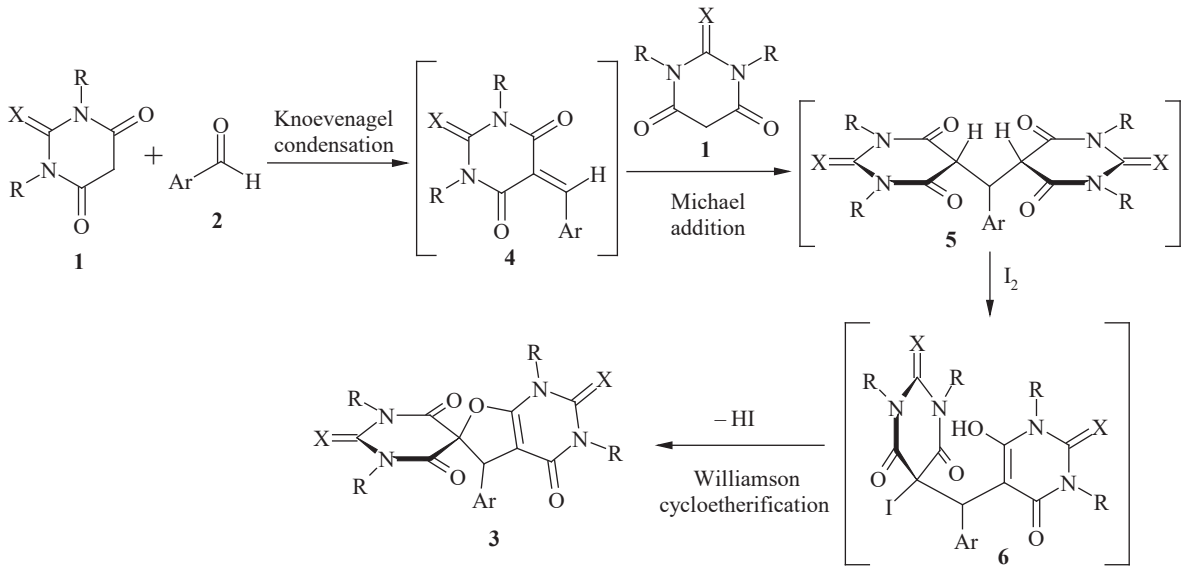
a R^2 = H, **b** R^2 = 3-OH
c R^2 = 4-Br, **d** R^2= 4-Cl
e R^2 = 4-F, **f** R^2 = 2-NO_2
g R^2 = 3-NO_2, **h** R^2 = 2-Cl
i R^2 = 3-Cl, **j** R^2 = 4-NO_2
k R^2 = 4-CN

3a-v

	R^1	X	R^2	Yield (%)	[Ref.]
3a	H	O	H	90	9
3b	H	O	3-OH	88	9
3c	H	O	4-Br	91	9
3d	H	O	4-Cl	90	9
3e	H	O	4- F	93	9
3f	H	O	2-NO_2	90	-
3g	H	O	3-NO_2	85	9
3h	H	S	H	81	-
3i	H	S	2-Cl	82	9
3j	H	S	3-Cl	79	-
3k	H	S	4-Cl	85	9

	R^1	X	R^2	Yield (%)	[Ref.]
3l	H	S	4-NO_2	88	9
3m	Me	O	H	92	7
3n	Me	O	4-CN	87	9
3o	Me	O	4-Cl	83	7
3p	Me	O	2-NO_2	90	9
3q	Me	O	3-NO_2	81	-
3r	Me	O	4-NO_2	93	7
3s	Me	O	4-F	94	9
3t	Et	S	H	77	9
3u	Et	S	4-Cl	79	9
3v	Et	S	4-NO_2	78	9

Scheme 1 The synthesis of oxospirotricyclic furobarbiturates **3**.



Scheme 2 Plausible reaction scenario for the formation of oxospirotricyclic furobarbiturates **3**.

type fashion to produce an aryl-bis(barbitur-5-yl)methane **5**. Subsequently, iodination of the Michael-adduct **5** gives a substituted 5-iodo-5-[aryl(barbitur-5-yl)methyl]pyrimidine **6**. Finally, intramolecular Williamson cycloetherification of **6** gives the oxospirotricyclic furobarbiturate **3**.

In order to gain an insight into a possible reaction mechanism, the 5-benzylidenebarbituric acid as a representative Knoevenagel condensation adduct was synthesised separately by the condensation of benzaldehyde and barbituric acid.[15] Then we examined the reaction of the isolated 5-benzylidenebarbituric acid with one equivalent of barbituric acid in the presence of one equivalent of molecular iodine in water at room temperature and we obtained the product **3a** in excellent yield within 4 h.

In summary we have developed a simple one-pot pseudo three-component synthesis of 5-aryl-1,5-dihydro-2*H*,2'*H*-spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine} derivatives, by the coupling of benzaldehydes and barbituric acid derivatives in water, promoted by molecular iodine as a mild oxidant. In comparison to another method,[7] this protocol has several advantages such as a clean reaction, easy operation, low cost, simple purification and improved yields. Furthermore, it can be considered as environmentally friendly, since it uses water as the reaction medium and purification is done by simple filtration and washing, avoiding the use of organic solvents at any point of the experimental procedure. More importantly the purification of compounds by a non-chromatographic method makes this process very significant for academic research and practical applications. In this experimentally simple process three new bonds (two C–C and one C–O) and one stereocentre are generated in a single operation with all reactants efficiently utilised. From the synthetic perspective, this reaction represents a major achievement in the synthesis of new biologically interesting oxospirotricyclic furobarbiturates containing unsubstituted (thio)barbituric acids or 1,3-diethyl-2-thiobarbituric acid moieties.

Experimental

The products **3a**–**e**, **3g**, **3i**, **3k**–**p** and **3r**–**v** are known compounds which were characterised using IR and ^{1}H NMR spectroscopy and their melting points were compared with literature values.[7,9] The products **3f**, **3h**, **3j** and **3q** are new compounds. Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an Elementar Vario EL III instrument. FTIR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz respectively, with $CDCl_3$ or DMSO-d_6 as solvents and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in parts per million (ppm) relative to TMS as an internal reference. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualised with UV light. All chemical reagents were obtained from Merck, Fluka or Acros and were used without further purification.

General procedure for the synthesis of **3a**–**v**

A mixture of barbituric acid derivative **1** (2.0 mmol), the appropriate benzaldehyde **2** (1.0 mmol), molecular iodine (1.0 mmol) and distilled water (10 mL), was taken in a 50 mL round bottom flask. The mixture was stirred at room temperature (25 °C) for 4 h. After completion of the reaction (monitored by TLC using EtOAc–hexane 1:1 as eluent), the reaction mixture was filtered off and the resulting precipitate was washed with water to afford the crude products **3**. Eventually, the crude product was purified by recrystallisation from ethanol. The dried products thus obtained each showed a single spot on TLC and were pure enough for all analytical purposes.

*5-(2-Nitrophenyl)-1,5-dihydro-2*H,*2'*H-*spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine}-2,2',4,4',6'(1'*H,*3*H,*3'*H*)-pentone* (**3f**): Cream powder; yield 0.349 g (90%); m.p. 335–337 °C; IR (KBr) (ν_{max} cm^{-1}): 3204, 3108 and 3080 (N–H), 1774, 1717 and 1648 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 5.12 (1 H, s, CH), 7.56–7.64 (2 H, m, arom), 8.06–8.17 (2 H, m, arom), 10.90, 11.06, 11.64 and 12.80 (4 H, 4 s, 4 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 167.7, 166.1, 165.1, 161.1, 152.2, 150.5, 148.7, 138.8, 137.1, 131.1, 124.9, 124.7, 90.1, 86.6, 55.1. Anal. calcd for $C_{15}H_9N_5O_8$ (387.26): C, 46.52; H, 2.34; N, 18.08; found: C, 46.39; H, 2.36; N, 18.11%.

*5-Phenyl-2,2'-dithioxo-1,5-dihydro-2*H,*2'*H-*spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine}-4,4',6'(1'*H,*3*H,*3'*H*)-trione* (**3h**): White powder; yield 0.278 g (81%); m.p. 288–290 °C; IR (KBr) (ν_{max} cm^{-1}): 3573, 3460, 3221 and 3150 (N–H), 1714 and 1661 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 4.74 (1 H, s, CH), 7.09–710 (2 H, m, arom), 7.25–7.26 (3 H, m, arom), 10.80, 11.02, 11.90 and 12.60 (4 H, 4 s, 4 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 168.2, 165.6, 165.0, 161.1, 152.0, 150.6, 135.9, 130.1, 129.6, 129.4, 90.5, 86.9, 56.9. Anal. calcd for $C_{15}H_{10}N_4O_4S_2$ (374.39): C, 48.12; H, 2.69; N, 14.96; found: C, 47.97; H, 2.72; N, 15.00%.

*5-(3-Chlorophenyl)-2,2'-dithioxo-1,5-dihydro-2*H,*2'*H-*spiro{furo[2,3-*d*]pyrimidine-6,5'-pyrimidine}-4,4',6'(1'*H,*3*H,*3'*H*)-trione* (**3j**): Pale yellow powder; yield 0.323 g (79%); m.p. 291–293 °C; IR (KBr) (ν_{max} cm^{-1}): 3300, 3234, 3140 and 3068 (N–H), 1735, 1706, 1680 and 1648 (C=O); ^{1}H NMR (400.2 MHz, DMSO-d_6): δ_H 5.10 (1 H, s, CH), 7.17–7.27 (1 H, m, arom), 7.29–7.35 (2 H, m, arom), 7.36–7.48 (1 H, m, arom), 10.94, 11.30, 11.77 and 12.70 (4 H, 4 s, 4 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 167.4, 165.1, 164.0, 160.1, 151.2, 149.9, 133.8, 132.5, 132.0, 130.7, 129.6, 127.7, 88.4, 86.0, 51.7. Anal. calcd for $C_{15}H_9ClN_4O_4S_2$ (408.84): C, 44.07; H, 2.22; N, 13.70; found: C, 43.88; H, 2.19; N, 13.71%.

*1,1',3,3'-Tetramethyl-5-(3-nitrophenyl)-1,5-dihydro-2*H,*2'*H-*spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]-2,2',4,4',6'(1'*H,*3*H,*3'*H*)-pentone* (**3q**): Cream powder; yield 0.359 g (81%); m.p. 275–277 °C; IR (KBr) (ν_{max} cm^{-1}): 1674 and 1667 (C=O); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 2.53, 3.07, 3.20 and 3.36 (12 H, 4 s, 4 NMe), 5.34 (1 H, s, CH), 7.48–7.55 (1 H, m, arom), 7.56–7.59 (1 H, m, arom), 7.64–7.68 (1 H, m, arom), 7.97–7.99 (1 H, m, arom); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 166.6, 164.0, 163.9, 159.1, 152.1, 151.3, 149.6, 134.8, 133.8, 131.5, 129.7, 125.9, 89.6, 87.2, 51.9, 31.0, 30.1, 29.2, 28.9. Anal. calcd for $C_{19}H_{17}N_5O_8$ (443.36): C, 51.47; H, 3.86; N, 15.80; found: C, 51.60; H, 3.85; N, 15.81%.

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References

1 S.L.Y. Tang, R.L. Smith and M. Poliakoff, *Green Chem.*, 2005, **7**, 761.
2 P.T. Anastas and J.C. Warner, *Green chemistry: theory and practice*. Oxford University Press, Oxford, England, 1998.
3 C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68.
4 P.T. Parvatkar, P.S. Parameswaran and S.G. Tilve, *Chem. Eur. J.*, 2012, **18**, 5460.
5 R.G. Melik-Ogandzhanyan, V.E. Khachatryan and A.S. Gapoyan, *Russ. Chem. Rev.*, 1985, **54**, 262.
6 N.N. Kolos, B.V. Kibkalo, L.L. Zamigaylo, I.V. Omel´chenko and O.V. Shishkin, *Russ. Chem. Bull.,* 2015, **64**, 864.
7 M.N. Elinson, A.N. Vereshchagin, N.O. Stepanov, P.A. Belyakov and G.I. Nikishin, *Tetrahedron Lett.*, 2010, **51**, 6598.
8 A.N. Vereshchagin, M.N. Elinson, E.O. Dorofeeva, T.A. Zaimovskaya, N.O. Stepanov, S.V. Gorbunov, P.A. Belyakov and G.I. Nikishin, *Tetrahedron*, 2012, **68**, 1198.
9 M.B. Teimouri, P. Akbari-Moghaddam and M. Motaghinezhad, *Tetrahedron*, 2013, **64**, 6804.
10 M.B. Teimouri, T. Abbasi and H.R. Khavasi, *J. Chem. Res.*, 2010, **34**, 310.
11 M.B. Teimouri, T. Abbasi and H. Mivehchi, *Tetrahedron*, 2008, **64**, 10425.
12 M.B. Teimouri and R. Bazhrang, *Monatsh. Chem.*, 2008, **139**, 957.
13 M.B. Teimouri and H. Mivehchi, *Synth. Commun.*, 2005, **35**, 1835.
14 R.G. Sheldon, *Green Chem.*, 2005, **7**, 267.
15 M. Deb and P.J. Bhuyan, *Tetrahedron Lett.*, 2005, **46**, 6453.