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Antimony trichloride catalyzed three-component reaction of urea, aldehydes and cyclic enol ethers: a novel route to 4-arylhexahydrofuro[2,3-*d*]pyrimidin-2(3*H*)-ones

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4-Arylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones

ABSTRACT

Antimony trichloride efficiently catalyses diastereoselective three-component reaction of urea, aromatic aldehydes and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran leading to 4-arylhexahydrofuro[2,3-*d*]pyrimidin-2(3*H*)-ones and 4-arylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones, respectively in good yield.

Multicomponent coupling reactions (MCRs) offer significant advantages over classical stepwise methods, because they offer rapid and convergent construction of complex molecules without the need of isolation and purification of any of the intermediates, resulting in substantial minimization of waste, labour, time and cost.[1] It is a process that triggers the conversion of three or more starting materials in one-pot to a product displaying large molecular diversity containing functional group characteristics of all the precursors. Thus, such reactions are economically and environmentally more attractive and have become an important tool in modern organic synthesis. They lead to one-pot atom-economic synthesis of highly functionalised molecules, which in many cases are of pharmacological importance capable of controlling enzymatic and other biological functions. These molecules are accessible more easily and economically than the biological therapeutics. With drug-like skeletal structure capable to fit specific receptors, they usually exhibit enhanced bioactivity, especially orally.[2] By the use of MCR, it is possible to build up a library of molecules useful to establish the nature of a pharmacophore and hence the molecule of maximum bioactivity.

Fused ring pyrimidinones have shown a broad spectrum of pharmacological activities and have attracted the interest of synthetic organic chemists over the years.[3] They have antibacterial, antitumor, antihypertensive, cardiotonic, bronchodilator, antiallergic, antimalarial, analgesic and even herbicidal properties in some cases.[4–11] However, there had been less exploration of the pharmacological properties of hexahydrofuropyrimidinones due to the absence of a convenient synthetic route. Therefore, these type of compounds attracted much attention due to their importance for QSAR study of fused ring pyrimidinones. Recently, Wu and coworkers disclosed[12] a novel three-component, one-pot reaction involving alkynes, urea or thiourea and aldehydes for the synthesis of pyrimidinones derivatives mediated by TMS-Cl. Very recently, Pandey et. al. explored[13] a simple and efficient organocatalytic multicomponent reaction involving 3,4-dihydro-(2*H*)-pyran, aromatic aldehydes and urea/thiourea as substrates and L-proline/TFA as catalyst to afford hexahydropyrano pyrimidinones (thiones) in good yields. With this background, in our effort to investigate the scope of antimony trichloride as a mild Lewis acid catalyst in organic synthesis,[14] we were prompted to find a general synthetic route towards 4-arylhexahydrofuro[2,3-*d*]pyrimidin-2(3*H*)-ones and homologous 4-arylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones by a MCR involving urea, aldehydes and cyclic enol ethers (Fig. 1).

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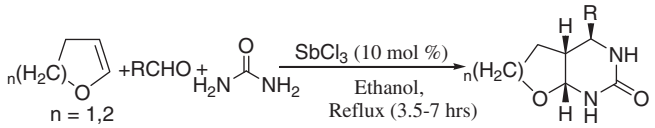


Figure 1. Synthetic route to pyrano and furano pyrimidinones.

We report herein an efficient synthetic route for the preparation of pyrano and furano[2,3-*d*]pyrimidinone derivatives in excellent yield catalysed by $SbCl_3$ and to the best of our knowledge this is the first report of the use of antimony trichloride as a catalyst for the synthesis of these type of compounds. Initially, we carried out the reaction between benzaldehyde, urea and 2,3-dihydrofuran using different catalysts-solvents combinations in order to find optimal reaction conditions. The results are summarised in Table 1.

From Table 1, it is evident that antimony trichloride and ethanol was found to be the most effective catalyst and solvent respectively both in terms of reaction time and yield. The reaction also proceeds at room temperature but was very slow (Table 1, entry 11). The progress of the reaction was marked by the appearance of a reddish colour. The optimum quantity of catalyst was screened and it was found that on increasing the amount of catalyst from 5 mol % to 10 mol %, yield of the reaction increases gradually but beyond 10 mol % there is no significant improvement of the rate as well as yield of the reaction. Replacing urea with thiourea did not produce the corresponding thio-derivative, instead a complex reaction mixture was obtained which could not be characterised. The reason for not producing the desired product with thiourea is probably due to the deactivation of the catalyst which needs to be studied in detail. To explore the scope of the reaction, we carried out reactions with various substituted aromatic aldehydes.

The relative stereochemistry was unequivocally determined by the nOe and NOESY experiments and by the X-ray crystallographic analysis (Fig. 2) of compound **3b**.[17] In nOe difference spectrum of **3e** in deaerated DMSO-d_6 solvent, significant enhancement was observed for the hydrogen at C-9 on irradiation of C-10 hydrogen, which confirmed the *cis* stereochemistry of ring fusion.

X-ray structure provided a direct evidence of the *cis* fused ring juncture. Crystallization was done in mixed solvent of ethanol and ethyl acetate by slow evaporation process. In fact each unit cell

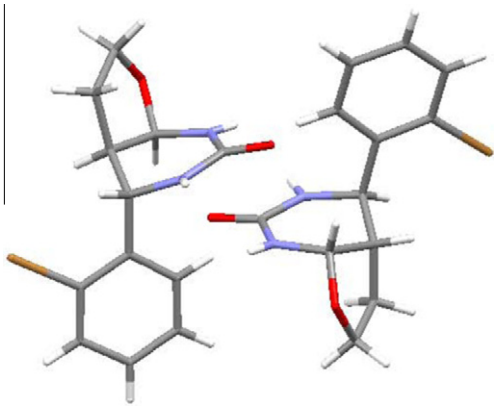


Figure 2. X-ray structure of enantiomeric **3b** molecule in a unit cell.

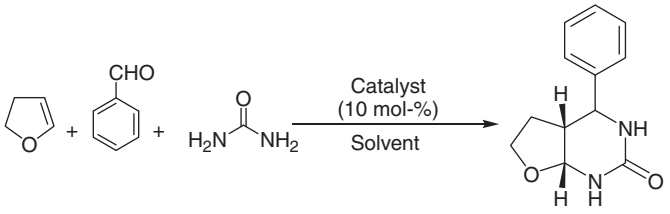
contained two molecules, an enantiomeric pair maintaining a centre of symmetry between them.

Notably, only a single diastereomer was formed from the reactions employing aldehydes **2a**–**e,** in spite of three consecutive chiral centres being present in the molecule. This could be explained by the proposed mechanism in light of work by Wu and coworkers[12] Initially, a condensation reaction occurs between urea and aldehyde to form *N*-acyliminium species which then undergoes nucleophillic attack by 2,3-dihydrofuran at the imine carbon to yield an oxonium intermediate with a diastereotopic face. Now the cyclization occurs by attack of the NH_2 group in an *exo* fashion, *endo* attack being disfavoured as the electrophillic cabon in question is spatially much away from the NH_2 group.

However, the aromatic aldehydes having a nitro group led to diastereomeric mixtures (Table 2, entries 6 and 7). The ratio of isomers was determined from their ^{1}H NMR spectrum. In case of 2,6-dichlorobenzaldehyde (**2c**) no diastereomeric mixture was formed (Table 2, entry 3). So it might be apprehended that the reaction is very much dependant on the electronic nature of the substituents on the aromatic ring.

Encouraged by these results, we performed reactions between urea, aldehydes and 3,4-dihydro-2*H*-pyran in an effort to build up similar 4-arylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one motifs (Table 3). Good to very good yields were obtained with

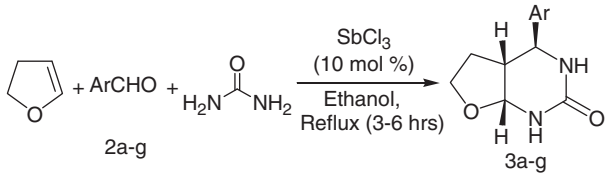
Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	$ZnCl_2$	C_2H_5OH	78	10	[c]
2	$ZnCl_2$	CH_3CN	82	10	[c]
3	CH_2SO_4	C_2H_5OH	78	10	Trace
4	CAN	C_2H_5OH	78	10	36
5	*p*-TsoH	CH_3CN	82	10	45
6	*p*-TsoH	C_2H_5OH	78	10	26
7	$SbCl_3$	CH_3CN	82	8	79
8	$SbCl_3$	C_2H_5OH	78	4	92
9	$SbCl_3$	Toluene	110	10	Trace
10	$SbCl_3$	CH_3NO_2	100	10	[c]
11	$SbCl_3$	C_2H_5OH	rt	72	55

[a] Reaction conditions: urea (1.2 mmol), benzaldehyde (1.0 mmol) in 3 ml solvent, catalyst (0.1 mmol), 2,3-dihydrofuran (1.5 mmol), reflux.
[b] Pure, isolated yield after column chromatography.
[c] Desired product not formed.

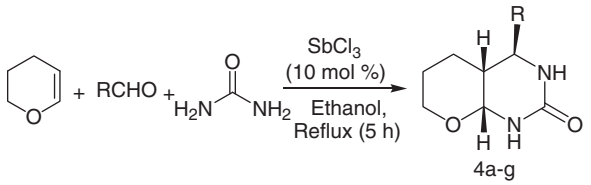
Table 2
Diastereoselective synthesis of 4-aryl hexahydro furo[2,3-*d*]pyrimidin-2(3*H*)-one[a,b]



Entry	Ar	Time (h)	Product	Yield[c] (%)
1	Phenyl	4.0	**3a**	92
2	2-Bromophenyl	3.5	**3b**	91
3	2,6-Dichlorophenyl	6.0	**3c**	81
4	4-Fluorophenyl	4.5	**3d**	92
5	4-Methoxyphenyl	3.5	**3e**	86
6	4-Nitrophenyl	3.0	**3f**[d]	88
7	2-Nitrophenyl	3.0	**3g**[e]	93

[a] Reaction condition: urea (1.2 mmol), aromatic aldehydes (1.0 mmol), $SbCl_3$(0.1 mmol), 2,3-dihydrofuran (1.5 mmol).[15,16]
[b] All compounds were characterised by ^{1}HNMR, ^{13}CNMR, HRMS, IR.
[c] Yield refers to pure and isolated yield.
[d] 2:1 Diastereomeric mixture obtained.
[e] 10:1 Diastereomeric mixture obtained.

Table 3
Preparation of 4-arylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones[a,b]



Entry	R	Product	Yield[c] (%)
1	Phenyl	**4a**	88
2	4′-Methylphenyl	**4b**	88
3	4′-Chlorophenyl	**4c**	91
4	4′-Methoxyphenyl	**4d**	94
5	4′-Nitrophenyl	**4e**	93
6	4′-Hydroxy-3′methoxyphenyl	**4f**	85
7	*E*-Styryl	**4g**	82

[a] Reaction conditions: urea (1.2 mmol), aromatic aldehydes (1.0 mmol), $SbCl_3$(0.1 mmol), 3,4-dihydro-2*H*-pyran (1.5 mmol).
[b] All compounds were characterised by ^{1}HNMR, ^{13}CNMR, HRMS, IR.
[c] Yield refers to pure and isolated yield.

excellent diastereoselectivity. In all the cases, only a single diastereomer was obtained.

Thus $SbCl_3$ has been proved to be a superior and mild Lewis acid catalyst in terms of economy, handling, reaction time and yield compared to the earlier literature.[12,13] It also showed tolerance to free phenolic hydroxyl group as in **4f**. The reaction was also smooth employing an α,β unsaturated aldehyde with no side reactions to yield **4g**.

In summary, we have developed a mild and efficient reaction between urea, aldehydes and cyclic enol ethers leading to 4-arylhexahydrofuro[2,3-*d*]pyrimidin-2(3*H*)-ones and homologous 4-arylhexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones using catalytic $SbCl_3$ with high atom economy. The notable advantages of this method are operational simplicity, use of inexpensive $SbCl_3$ catalyst, mild reaction conditions, ease of isolation of products and non-toxic ethanol as solvent. Due to easy availability of the starting materials, the reaction might prove to be very useful for building up pyrimidine scaffolds. Further studies in this area to explore the synthetic applications of the reaction are being carried out in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.064.

References and notes

1. (a) Balme, G.; Bosshart; Monteiro, E. N. *Eur. J. Org. Chem.* **2003**, 4101–4111; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80; (c) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471–1499; (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144; (e) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329; (f) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *112*, 3168–3210; (g) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564; (h) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1694; (i) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (j) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley: VCH:Weinheim, 2000; pp 39–64.
2. (a) Padwa, A. In *Progress in Heterocyclic Chemistry*; Suschitzky, H., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1994; Vol. 6, pp 36–55; (b) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141–2153.
3. (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898–5907; (b) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803–2816; (c) Zhu, Y.; Huang, S.; Pan, Y. *Eur. J. Org. Chem.* **2005**, 2354–2367.
4. *The Pyrimidines*; Fenn, D., Ed.; Wiley: New York, NY, 1994.
5. Ghorab, M. M.; Hassan, A. Y. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *141*, 251.
6. Coates, W. J. Eur. Patent 351058, 1990.
7. (a) Fosseheim, R.; Svarteng, K.; Mostad, A.; Romming, C.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1982**, *25*, 126–131; (b) Levitt, G. U.S. Patent 4,339,267, 1982.; (c) Love, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1974**, *17*, 965.
8. (a) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095–1099; (b) Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327–329.
9. Davoll, J.; Clarke, J.; Elslager, E. F. *J. Med. Chem.* **1972**, *15*, 837–839.
10. Furuya, S.; Ohtaki, T. Eur. Patent 608565, 1994.
11. Kitamura, N.; Onishi, A. Eur. Patent 163599, 1984.
12. Zhu, Y.; Huang, S.; Wan, J.; Yan, L.; Pan, Y.; Wu, A. *Org. Lett.* **2006**, *8*, 2599–2602. and the references cited therein.
13. Pandey, J.; Anand, N.; Tripathi, R. P. *Tetrahedron* **2009**, *65*, 9350–9356. and the references cited therein.
14. (a) Russowsky, D.; Canto, R. F. S.; Sanches, S. A. A.; D'Oca, M. G. M.; Fátima, Â.; Pilli, R. A.; Kohn, L. K.; Antônio, M. A.; Carvalho, J. E. *Bioorg. Chem.* **2006**, *34*, 173–182; (b) Cepanec, I.; Litvić, M.; Filipan-Litvić, M.; Grüngold, I. *Tetrahedron* **2007**, *63*, 11822–11827; (c) Maiti, G.; Kundu, P. *Tetrahedron Lett.* **2006**, *47*, 5733–5736; (d) Maiti, G.; Kundu, P. *Synth. Commun.* **2007**, *37*, 2309–2316; (e) Bhattacharya, R. N.; Kundu, P.; Maiti, G. *Synth. Commun.* **2010**, *40*, 476–481.
15. *Representative experimental procedure for the synthesis of 4-arylhexahydrofuro[2,3-d]pyrimidin-2(3H)-one* (**3a**): To a solution of benzaldehyde (106 mg, 1 mmol) in 3 ml ethanol, urea (72 mg, 1.2 mmol) was added and stirred at room temperature for 15 min. To this stirred solution, $SbCl_3$ (22 mg, 0.1 mmol) was added followed by addition of 2,3-dihydrofuran (105 mg, 1.5 mmol) and was refluxed for 4 h fitted with a reflux condenser and a calcium chloride guard tube. The progress of the reaction was followed by TLC. After completion of the reaction, the volatiles were removed under reduced pressure and the product was purified by column chromatography over silica gel (60–120) eluting with 50% ethyl acetate in hexane to afford **3a** (200 mg, 0.92 mmol, 92%) as a white crystalline solid; mp 200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62–1.67 (m, 1H), 1.87–1.99 (m, 1H), 2.28 (t, J = 3.8 Hz, 1H), 3.65 (dd, J = 8.5, 13.9 Hz, 1H), 3.91 (dd, J = 8.0, 15.0 Hz, 1H), 4.10 (d, J = 7.8 Hz, 1H), 4.80 (t, J = 3.9 Hz, 1H), 6.80 (s, 1H), 7.18 (s,1H), 7.25–7.40 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.5, 41.6, 55.0, 63.9, 83.4, 127.7, 128.0, 128.9, 142.1, 155.8. HRMS: calcd for $C_{12}H_{14}N_2NaO_2$ 241.0953; found 241.0956.
16. This protocol was followed for all reactions listed in Table 2 and Table 3 except otherwise stated with reaction times listed thereof.
17. *Selected X-ray crystallographic data for compound* **3b**: $C_{12}H_{13}BrN_2O_2$, rectangular, a = 7.1060(14) Å, b = 13.373(3) Å, c = 25.901(5) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 2461.3(9) Å^3. CCDC-778922 contains the Supplementary crystallographic data for the structure reported in this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.