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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5407–5409

$TaBr_5$-catalyzed Biginelli reaction: one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones under solvent-free conditions

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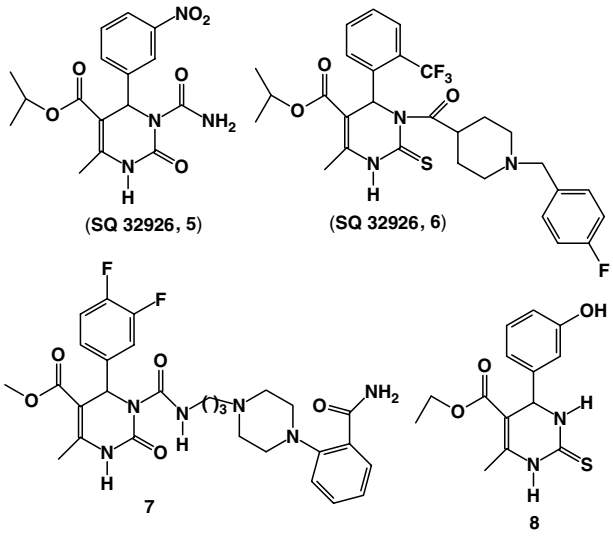
Received 31 January 2007; accepted 5 June 2007
Available online 9 June 2007

Abstract—An efficient $TaBr_5$ (5–10 mol %)-catalyzed Biginelli reaction under solvent-free conditions for one-pot syntheses of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their thione analogs is reported. The catalyst is stable at room temperature and employed under mild and environmentally friendly conditions.

Synthetic modifications in which highly functionalized organic molecules can be produced from easily available substrates via atom-efficient reactions have special importance for the organic chemists, for example, in expeditious domino and multicomponent reactions (MCRs).[1] In these reactions, three or more reactants are combined to form a new product that contains moieties of all components.[2] The Biginelli reaction[3] is one of the most useful examples of MCRs, gaining increasing importance in organic and medicinal chemistry due to their capacity to generate multifunctionalized products including 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs), their thiones analogs and other related heterocyclic compounds. Such heterocycles (Scheme 1) show a wide range of pharmacological properties including antiviral, antitumor, antibacterial and anti-inflammatory activities.[4] Recently, appropriately functionalized DHPM analogs have emerged as orally active antihypertensive agents (**5**, **6**)[5] and α_{1a} adrenoceptor-selective antagonists (**7**).[6] An other highlight in this context has been the identification of the structurally rather simple DHPM monastrol (**8**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells causing cell cycle arrest.[7]



Scheme 1.

To enhance the efficiency of the Biginelli reaction/condensation, various catalysts and reaction conditions have been studied including classical conditions with microwave-assisted irradiation,[8] solid-support,[9] ionic liquids,[10] Lewis and protic acid promoters such as concd HCl,[3a] concd H_2SO_4,[11a] $M(Cl)_2$ where M = Zn, Sn, Cu, Co, Ni,[11b] $InBr_3$,[11c] CuI,[11d] I_2,[11e] TMSI,[11f] $Ln(OTf)_3$ where Ln = Yb, Sc, La,[11g] $M(NTf)_2$ where M = Ni, Cu, Yb,[11h] $Ce(NO)_3{\cdot}6H_2O$,[11i] $CeCl_3{\cdot}7H_2O$,[11j] $RuCl_3$,[11k]

Keywords: $TaBr_5$-catalyzed Biginelli reaction; Solvent-free conditions; 3,4-Dihydropyrimidin-2-(1*H*)-ones/thiones.
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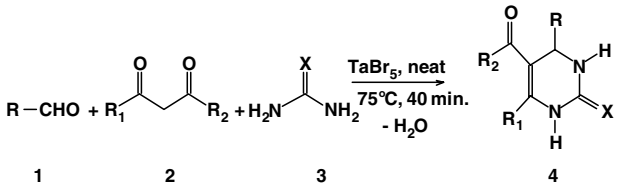
doi:10.1016/j.tetlet.2007.06.005



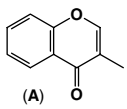
Scheme 2.

$ZrCl_4$,[11l] $LiBr_2$,[11m] $Co(OAc)_2$,[11n] $PhB(OH)_2$,[11o] *p*-TSA,[11p] $Ag_3PW_{12}O_{40}$,[11q] H_3BO_3,[11r] HBF_4,[11s] chiral phosphoric acid,[11t] and bases like NH_4Cl,[12a] $KHSO_4$.[12b] These catalysts have been efficiently used both on solid-support and in organic or aqueous solutions. However, some of these catalyzed conditions have drawbacks, for example, the need of strong and protic acids,[3a,11a] anhydrous conditions,[11g–k] high temperature and prolonged reaction times.[10,11q] To overcome such obstacles (that may translate in environmental concerns), chemists are challenged to develop clean procedures that avoid harmful organic solvents or completely eliminate the latter. This prompted us to search for improved and more efficient catalytic condition for the Biginelli reaction.

In continuation of our interest in Lewis acid applications for different organic reactions and the salient features of $TaBr_5$ in solid-supported synthesis (where it acts as a better Lewis acid than in solution), we evaluated the use of $TaBr_5$ as a novel Lewis acid catalyst for the Biginelli reaction. The use of $TaBr_5$ on solid-support increases the tantalum's oxophilicity resulting in rapid reaction rates, absence of unwanted products, improved and operational simplicity using conventional heating.[13] Here we report the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and thione analogs from the corresponding aldehydes, ethyl acetoacetate or ethyl trifluoroacetoacetate and urea or thiourea in the presence of tantalum(V) bromide under solvent-free conditions (Scheme 2).

Using a simple experimental procedure,[14] the $TaBr_5$-catalyzed Biginelli reaction of a wide range of reactants (**1**, **2** and **3**) gave the DHPMs and thione analogs (**4**) in high yield (Table 1). The procedure avoids problems associated with the use of organic solvents including handling, safety, pollution and monetary considerations. Decreased reaction times are also realized due to the increased reactivity of the reactants under neat condition as compared to the same reactions conducted in solvents such as ethyl acetate, ethanol, acetonitrile and dichloromethane. Furthermore, using silica gel or alumina as solid-support for the $TaBr_5$ in the above reactions resulted in the formation of various decomposition products.[13a] The presence of either electron-withdrawing or electron-donating substituents on the aldehydes did not

Table 1. $TaBr_5$-catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones under solvent-free conditions

Run	Reactants				Product (*m*/*z*, M^+)	Yield (%)[a,b]	Ref. [c]
	R	R_1	R_2	X			
1	C_6H_5–	Me	OEt	O	**4a** (260.28)	97	12b
2	C_6H_5–	Me	OEt	S	**4b** (276.35)	98	12b
3	4-Br–C_6H_5–	Me	OEt	O	**4c** (339.19)	85	11d
4	4-Br–C_6H_5–	Me	OEt	S	**4d** (355.25)	88	11d
5	3-O_2N–C_6H_5–	Me	OEt	O	**4e** (305.28)	91	12b
6	3-O_2N–C_6H_5–	Me	OEt	S	**4f** (321.35)	92	12b
7	3-F–C_6H_5–	Me	OEt	O	**4g** (278.27)	82	8c
8	3-F–C_6H_5–	Me	OEt	S	**4h** (294.34)	85	8c
9	4-O_2N–C_6H_5–	Me	OEt	O	**4i** (305.28)	96	12b
10	4-O_2N–C_6H_5–	Me	OEt	S	**4j** (321.35)	90	11s
11	4-HO–C_6H_5–	Me	OEt	O	**4k** (276.28)	82	9a
12	4-HO–C_6H_5–	Me	OEt	S	**4l** (292.35)	85	9a
13	4-F–C_6H_5–	CF_3	OEt	S	**4m** (348.32)	95	11l
14	3-O_2N–C_6H_5–	CF_3	OEt	O	**4n** (359.26)	92	11l
15	*trans*-C_6H_5–CH=CH–	Me	OEt	O	**4o** (286.33)	90	11s
16	*trans*-C_6H_5–CH=CH–	Me	OEt	S	**4p** (302.39)	94	9a
17	4-^{t}But–C_6H_5–	Me	OEt	O	**4q** (316.39)	90	11c
18	4-^{t}But–C_6H_5–	Me	OEt	S	**4r** (332.46)	94	11c
19	C_6H_5–	Me	$OCH_2C_6H_5$	S	**4s** (338.42)	90	12b
20	 (A)	CF_3	OEt	O	**4t** (382.07)	82	12c
21	**A**	Me	$OCH_2C_6H_5$	S	**4u** (406.10)	82	12c
22	**A**	Me	OEt	O	**4v** (328.11)	84	12c
23	**A**	Me	$OCH_2C_6H_5$	O	**4w** (390.12)	80	12c
24	C_6H_5–	CF_3	OEt	S	**4x** (330.32)	97	11l

[a] Substrates **1**, **2** (2.0 mmol), **3** (1.5 mmol), and $TaBr_5$ (5–10 mg, 5–10 mol %) were stirred at 70–80 °C for 40–45 min.
[b] Isolated and non-optimized yield.
[c] Identification of the products was ascertained by ^1H and ^{13}C NMR, mass spectroscopy and comparison with available Mp and spectroscopic lit. data.

affect their reactivity or product yield. The assigned structures of the products were established from their spectral properties (^{1}H and ^{13}C NMR, and MS) and also by comparison with available literature data (Table 1).

In conclusion, we have shown an efficient $TaBr_5$-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and thione analogs (**4**) by multicomponent Biginelli reactions under solvent-free conditions, using commercially available substrates and tantalum salt. The advantages of this procedure over earlier reported processes include its simplicity, fast and clean reactions, high yield, and the absence of organic solvent.

Acknowledgment

This work was supported by the Canadian Institutes of Health Research (CIHR, grant MOP- 44065).

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14. *General Procedure for the Biginelli reaction*: $TaBr_5$ (5–10 mol %) was added to a stirred mixture of aldehydes (2.0 mmol), ethyl acetoacetate or ethyl trifluoroacetoacetate (2.0 mmol) and urea or thiourea (1.5 mmol) in solvent (i.e. dichloromethane/ethanol/ethyl acetate/acetonitrile, 1–1.5 ml) under argon and further stirred for 5–10 min to complete dissolution of $TaBr_5$. The solvent was gradually evaporated by heating and the neat reaction mixture was heated with stirring for 40–45 min at 70–80 °C. Product precipitation started after 15 min, TLC monitoring showed that the reaction was completed after 45 min. After cooling the solid precipitate was filtered and washed with cold water and ethanol under reduced pressure and the residue was crystallized from ethanol or ethyl acetate–hexane (1:3) to afford the pure product (**4**).