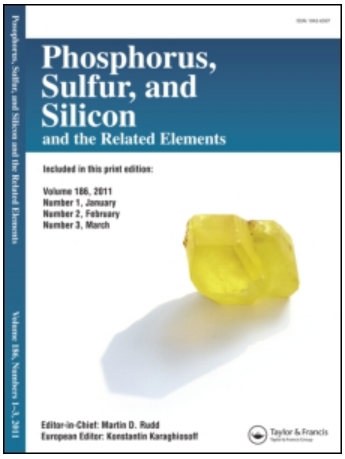

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Titanium(IV) Chloride Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*h*)-ones under Solvent-Free Conditions via Three-Component Biginelli Reaction

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Titanium(IV) Chloride Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*h*)-ones under Solvent-Free Conditions via Three-Component Biginelli Reaction

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An efficient and cost-effective method has been developed for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones by a one-pot three-component cyclocondensation reaction of a 1,3-dicarbonyl compound, an aldehyde, and (thio)urea using titanium(IV) chloride as catalyst under solvent-free conditions. Addition of $TiCl_4$ to a mixture of the neat reactants afforded the products more quickly and in better yields as compared to traditional methodologies. This methodology presents an improvement of the classical Biginelli three-component condensation, and it is more convenient being inexpensive and proceeding under milder conditions and with shorter reaction times.

Keywords Biginelli reaction; dihydropyrimidin-2(1*H*)-ones; solvent-free conditions

INTRODUCTION

Multicomponent reactions (MCR) are of increasing importance in organic and medicinal chemistry for various reasons.[1] Multicomponent condensation involves three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. More than a century ago, Biginelli intuitively anticipated the synthetic potential of multicomponent reactions by combining in a single flask the reactants of two different reactions having one component in common.[2] In recent years, there has been increasing interest in the design of alkyl 1,4-dihydropyrimidine-5-carboxylates (1,4-DHPMs) and related Biginelli-like compounds,[3]

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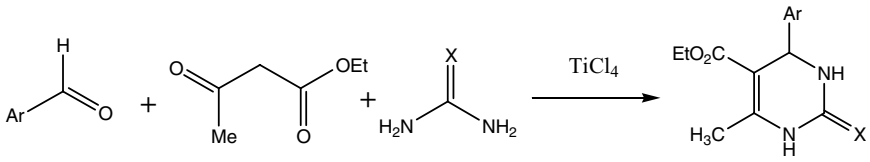
which may act as valuable substitutes[4] for the well-known Nifedipine and other 1,4-dihydropyridine drugs[5] clinically used in the treatment of cardiovascular diseases. That interest is illustrated, i.e., by the disclosure of elegant protocols involving solid-phase synthetic approaches,[6] as well as solvent-free preparations under microwave irradiation.[7]

A serious drawback of the original Biginelli reaction is the low yield in the case of substituted aliphatic and aromatic aldehydes.[8] Recently, several improved procedures[9] have been reported using Lewis acids, as well as protic acids as promoters. However, these methods involve expensive reagents, stoichiometric amounts of the catalyst, strong acidic conditions, long reaction times, high temperatures, unsatisfactory yields, and incompatibility with other functional groups. Some microwave-assisted Biginelli reactions have been reported giving better yields; they involve the use of polyphosphate ester (PPE)[10] or conc. HCl[11] as catalysts, or require sealed reaction vessels.[12]

In a conceptually different approach, Nichter, Ondruschka, et al. presented the parallel generation of a 36-member library of Biginelli dihydropyrimidines in a suitable multivessel rotor placed inside a dedicated multimode microwave reactor.[13,14] To the best of our knowledge, there are no reports regarding the application of $TiCl_4$ in the reaction with neat reactants for the preparation of Biginelli compounds. Here, we report for the first time the use of this reagent in the synthesis of dihydropyrimidinones. In view of the current emphasis on solid-state synthesis[15] and green chemistry,[16] there is a merit developing Biginelli reaction conditions in solvent-free systems. We have recently reported some green methods for the synthesis of several heterocyclic compounds.[17] In continuation of our interest in organic synthesis in solvent-free systems,[18] we report an alternative method for the solvent-free preparation of 3,4-dihydropyrimidin-2(1*H*)-ones using $TiCl_4$ as catalyst by the Biginelli reaction of a neat mixture of arylaldehydes, (thio)urea, and a ß-ketoester (Scheme 1).



1 **2** **(a-j)**

SCHEME 1

Ar, X: see Table I

TABLE I Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones via One-Pot Three-Component Biginielli Condensation

	Ar	X	Time (sec)	Mp (°C) Found	Mp (°C) Reported	Yield (%)[a]
2a	phenyl	S	60	203–205	202–204[20]	75
2b	2-furyl	S	50	206–207	208–210[21]	72
2c	2-indolyl	S	70	>300	>300[21]	65
2d	2-$NO_2C_6H_4$	O	50	202–203	206–208[20]	78
2e	2-OHC_6H_4	O	80	198–201	199–201[22]	65
2f	4-FC_6H_4	O	65	182–184	185–186[23]	78
2g	3-$NO_2C_6H_4$	S	55	203–205	206–207[20]	77
2h	4-OHC_6H_5	O	70	194–197	196–197[22]	65
2i	4-ClC_6H_4	O	70	210–213	213–215[23]	66
2j	3,4-$(MeO)_2C_6H_3$	O	90	175–177	178–178.5[24]	60

[a]After recrystallization.

EXPERIMENTAL

This procedure was further extended to the synthesis of the 4-(3-hydroxyphenyl)-2-thione derivative monastrol (**2h**),[19] a novel cell-permeable lead molecule for the development of new anticancer drugs.

All melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 843 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker Avance 500 or a JEOL FX90 instrument. Mass spectra were obtained with a Shimadzu QP 1100EX instrument. Elemental analyses were performed with a LECO CHNO-932 Analyzer instrument.

General Procedure

The catalyst (1 mmol) was added to a mixture of the aldehyde (10 mmol), (thio)urea (11 mmol), and the ß-keto ester (11 mmol). The reaction was essentially complete after the addition of the $TiCl_4$ within 90 sec (Table I). The reaction mixture was poured onto crushed ice and neutralized by aqueous NaOH. The resulting crude product was filtered off and recrystallized from hot 95% EtOH to afford the pure compound. All the products are known compounds, which were characterized by comparison of their melting points with the literature values.

REFERENCES

[1] (a) H. Bienayme, C. Hulme, G. Oddon, and P. Schmitt, *Chem. Eur. J.*, **6**, 3321 (2000); (b) A. Domling and I. Ugi, *Angew. Chem. Int. Ed.*, **39,** 3168 (2000).
[2] P. Biginelli, *Gazz. Chim. Ital.*, **23,** 360 (1893).

[3] C. O. Kappe, *Tetrahedron*, **49,** 6937 (1993).
[4] (a) H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda, T. Ishihara, K. Funahashi, F. Satoh, M. Morita, and T. Noguchi. *J. Med. Chem.*, **32,** 2399 (1989); (b) K. S. Atwal G. C. Rovnyak, J. Schwartz, S. Moreland, A. Hedberg, J. Z. Gougoutas, M. F. Malley, and D. M. Floyd, *J. Med. Chem*., **33,** 1510 (1990).
[5] F. Bossert, H. Meyer, and E. Wehinger, *Angew. Chem. Int. Ed. Engl*., **20,** 762 (1981).
[6] P. Wipf and A. Cunningham, *Tetrahedron Lett.*, **36,** 7819 (1995).
[7] C. O. Kappe, D. Kumar, and R. S. Varma, *Synthesis*, 1799, (1999).
[8] (a) K. Folkers, H. J. Harwood, and T. B. Johnson, *J. Am. Chem. Soc.*, **54,** 3751 (1932); (b) P. Wipf and A. Cunningham, *Tetrahedron Lett*., **36,** 7819 (1995).
[9] (a) Y. Qian, C. Ma, L. Wang, and M. Yang, *J. Org. Chem*., **65,** 3864 (2000); (b) J. Lu, H. Ma, *Synlett*, **1,** 63 (2000); (c) C. O. Kappe, *Tetrahedron*, **49,** 6937 (1993).
[10] C. O. Kappe, D. Kumar, and R. S. Varma, *Synthesis,* 1799 (1999).
[11] A. Stadler and C. O. Kappe, *J. Chem. Soc., Perkin Trans*., **2,** 1363 (2000).
[12] H. A. Stefani and P. M. Gatti, *Synth. Commun.*, **30,** 2165 (2000).
[13] M. Nichter and B. Ondruschka, *Mol. Diversity*, **7,** 253 (2003).
[14] M. Nichter, B. Ondruschka, A. Tied, W. Lautenschlager, and K. Borowski, *J. Am. Genomic/Proteomic Technol*., **1,** 34(2001).
[15] (a) B. C. Ranu, A. Hajra, and U. Jana, *J. Org. Chem.*, **65,** 6270 (2000); (b) Y. Ma, C. Qian, L. Wang, and M. Yang, *J. Org. Chem.*, **65,** 3864 (2000); (c) J. Lu and H. Ma, *Synlett*, **1,** 63 (2000); (d) C. O. Kappe, *Tetrahedron*, **49,** 6937 (1993).
[16] M. Balogh and P. Laszlo, *Organic Chemistry Using Clays*, (Springer, Berlin, 1993), and references cited therein.
[17] A. Shockravi, H. Valizadeh, and M. M. Heravi, *Phosphorus, Sulfur, and Silicon*, **177,** 2835 (2002).
[18] (a) A. Shockravi, H. Sharghi, H. Valizadeh, and M. M. Heravi, *Indian J. Heterocycl. Chem.*, **11,** 331 (2002); (b) A. Shockravi, H. Valizadeh, M. M. Heravi, and H. A. Ghadim, *J. Chem. Research* (*S*), 718 (2003); (c) H. Valizadeh, M. Mamaghani, and A. Badrian, *Synth. Commun.*, **35,** 785 (2005); (d) H. Valizadeh and A. Shockravi, *Tetrahedron. Lett.*, **46,** 3501 (2005); (e) H. Valizadeh and A. Shockravi, *J. Heterocycl. Chem.*, **43,** 1 (2006).
[19] T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, and T. J. Mitchison, *Science*, **286,** 971 (1999).
[20] P. Salehi, M. Dabiri, M. A. Zolfigol, and M. B. Bodaghi Fard, *Tetrahedron Lett.*, **44,** 2889 (2003).
[21] M. Kidwai, S. Saxena, R. Mohan, and R. Venkataramanan, *J. Chem. Soc., Perkin Trans.*, **1,** 1845 (2002).
[22] F. A. Lopes, V. S. S. da Silva, K. F. S. Canto, M. G. Montes, and M. N. Godoi, *J. Braz. Chem.*, **15,** 165 (2004).
[23] E. H. Hu, D. R. Sidler, and U. H. Dolling, *J. Org. Chem.*, **63,** 3454 (1998).
[24] K. Folkers, H. J. Harwood, and T. B. Jahnson, *J. Am. Chem. Soc.*, **54,** 3751 (1932).