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Original Article

An efficient, Method for the Synthesis of 4H-Pyrido-[1, 2]-Pyrimidine Derivatives and their anticancer activity

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ABSTRACT

A library of 4H-pyrido-[1,2]-pyrimidine derivatives were synthesised via one pot three component method, in this reaction involves a simple condensation of 2-minopyrimidines, aldehydes and ketones in the prescence of ethanol reflux by using cost effective and ecofriendly catalyst sulphamic acid. These synthesised compounds were submitted for the anti proliferative activity aganist various human cancer cell lines, among these 2,3, 8 and 12 compounds were showed excellent activity. Range between 1.15- 1.95 µM.

Keywords: Anti-Cancer, pyrimidine, Anti-proliferative

1. INTRODUCTION

The pyrimidine are having high sort in the medicinal chemistry to the development of novel active therapeutics. It has a wide range of interest in the pharmacology, [1, 2] such as antibacterial, antiviral including anti-HIV, anticancer, analgesic and anti-inflammatory properties.[3-6] Multicomponent reactions (MCRs) are implicated in various interesting and difficult conversion in organic synthesis[7-12], and it have much importance in the synthetic organic chemistry because of their generality of the products now these are called as precursors of the drug discovery. Most of the applications were already well-known those are Biginelli reaction, Mannich, Ugi reaction[13-15]. Whatever the development of novel multicomponent reaction have great need in the field of medicinal and synthetic organic chemistry for the generating novel active scaffolds, [16, 17]. As per our best of our knowledge there is no report of the synthesis of 4H-Pyrido-[1, 2]-pyrimidine derivatives by using this ecofriendly method, Here the catalyst can recyclable and reusable upto 3-4 times without any loss and properties of the Catalyst. Our present method develops and to prepare fourteen compounds of new heterocycles it extends to develop by willingly existing carbonyl compounds.

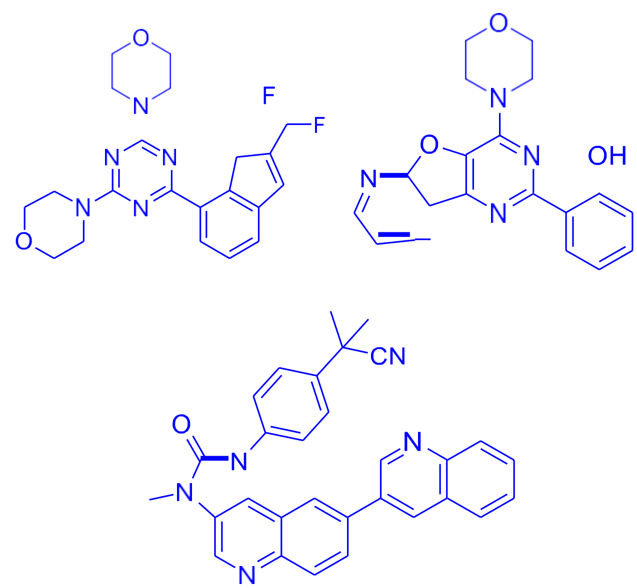

Fig: 1- biologically active pyrimidine derivatives

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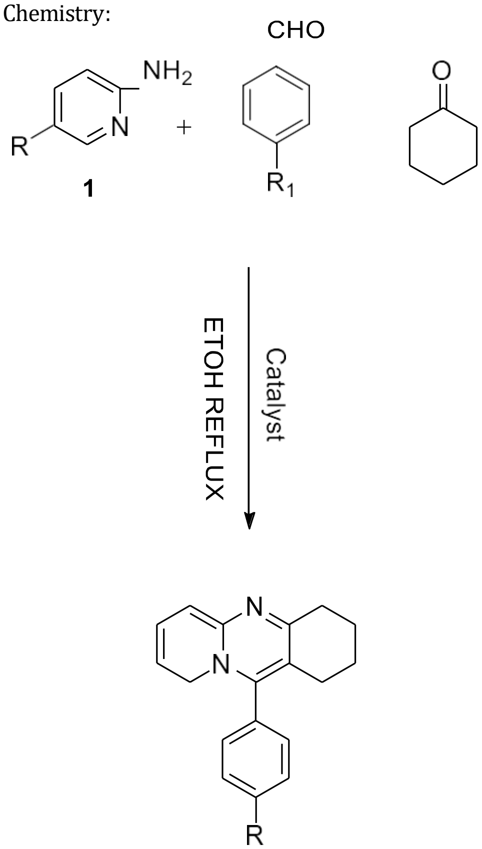
Results and discussions:

Chemistry:



Here model reaction was done with 2-amiopyridine (1.0 mmol), aldehydes (1.0 mmol) and ketones (2.0 mmol) by using sulpamic acid as a racycleble and reusable catalyst in the presence of ethanol as a solvent reflux then add catalyst , under nitrogen condition the reaction mixture was stirred with reflux for 5h this reaction was monitored by the TLC. After completion of the reaction. Then solvent Ethanol was removed from the reaction by rotavaccume pressure. Resultant reaction mixture extracts with ethyl acetate and water, the organic layer washed with sodium sulphate then it evaporate solid compound was formed then it was purifiedfied by the column chromatography by using Ethyl acetate and Hexane mobilephase, afforded final desired product (compound-1d). And yields are good to excellent.

Table-1: Optimization of reaction conditions for the synthesis of 4H-Pyrido-[1, 2]- pyrimidine derivatives.

S.no	Solvent	Temp-(°C)	Time (hr)	Yield %[a]
1	methanol	RT	12	20
2	water	RT	12	15
3	ethanol	RT	12	25
4	methanol	60	6	40
5	--------	120	6	50
6	**ethanol**	**80**	**5**	**80**
7	water	100	5	55
8	methanol	80	5	50

[a]-isolated yields

Table-1: Optimization of reaction conditions for the synthesis of 4H-Pyrido-[1,2]- pyrimidine derivatives.

S.No	R	R1	R2	Yield%a
1	H	H	H	70
2	H	4-CL	H	72
3	H	4-F	H	77
4	H	4-NO2	H	68
5	H	3-NO2	H	65
6	**H**	**3-Cl**	H	**70**
7	H	**3-F**	H	75
8	H	4-OME	H	78
9	H	4-Me	H	65
10	4-Cl	H	H	76
11	4-Cl	4-Cl	H	80
12	4-Cl	4-F	H	82
13	4-Cl	4-NO2	H	76
14	4-Cl	3-NO2	H	72

[a]-isolated yields

Table-2: Synthesis of 4H-Pyrido-[1, 2]-pyrimidine derivatives by condensation of 2- aminopyrimidines, aldehydes and ketones.

Mechanism:

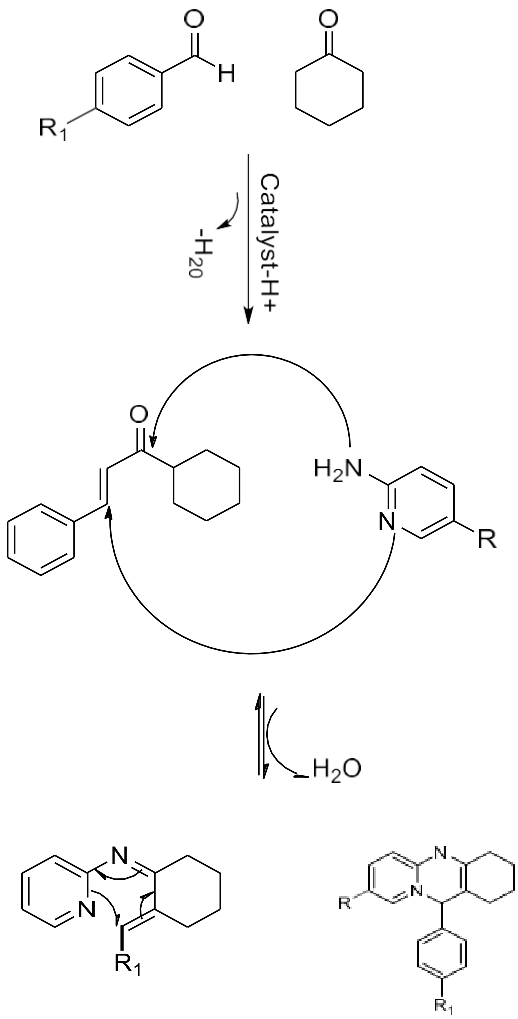


Fig 2: Mechanism for 4H-prido-[1,2-] pyramidine synthesis.

This procedure plausible mechanism for the formation of 4H-prido-[1,2-] pyramidine from 2- aminopyrimidines, aldehydes and ketones by using recyclable and reusable catalyst (sulphamic acid) shown in the figure-2 first aldehyde and acetophenones are couple then form intermediate with elimination of water molecule. Then this intermediate was reacts with 2-aminopyridine by using proton from acidic catalyst again it eliminates the water molecule, then final the double bond pi- electons of 2-aminopyridine migrates to the adehyde carbon finally cycled product was formed.

Antiproliferative activity

Cytotoxicity assay was performed 18 was performed to estimate the cytotoxic prospective of these compounds neighbouring to selected human cancer cell lines which include HeLa (cervical), (liver) A549, prostate (DU 145) and MCF-7 (breast). These compounds showed noteworthy cytotoxic activity with IC50 values ranging from 1.15-1.95 µM against different cancer cell lines. The results are concise as IC50 values in Table 3

S.no	A549	Temp-(°C)	Time (hr)	Yield %[a]
1	3.54	3.13	4.37	3.65
2	1.99	1.93	2.09	1.15
3	1.91	2.81	6.90	3.51
4	4.90	3.89	5.25	5.97
5	6.50	7.47	5.90	5.24
6	4.90	3.75	6.14	7.38
7	5.57	4.54	7.06	8.74
8	1.75	1.96	2.87	3.08
9	4.13	3.31	5.68	7.03
10	4.70	704	6.78	7.93
11	7.56	5.29	10.2	6.90
12	2.61	1.94	1.81	4.01
13	6.75	7.94	8.87	4.08
14	7.08	4.09	4.90	5.39
Control	1.31	1.81	2.13	1.25

Table. 3 Antiproliferative acivity for the synthesised derivatives

Experimental procedure:

The reaction was done with 2-amiopyridine (1.0 mmol), aldehydes (1.0 mmol) and ketones (2.0 mmol) by using sulpamic acid as a racycleble and reusable catalyst in the presence of ETOH as a solvent reflux then add catalyst , under nitrogen condition the reaction mixture was stirred with reflux for 5 hours this reaction was monitored by the TLC. After completion of the reaction. Then solvent Ethanol was removed from the reaction by rotavaccume pressure. Resultant reaction mixture extracts with ethyl acetate and water, the organic layer washed with sodium sulphate then it evaporate solid compound was formed then it was purifiedfied by the column chromatography by using Ethyl acetate and Hexane mobilephase, afforded final desired product . And yields are good to excellent.

11-(4-Nitrophenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline -1

77 %; white solid, mp: 148–151 oC; 1H NMR: δ 8.25–8.22 (m, 2H), 7.54–7.45 (m, 3H), 7.34–7.29 (m, 1H), 7.07 (d, 1H, J = 6.3), 6.46 (t, 1H, J = 6.3), 5.72 (s, 1H), 2.53–2.37 (m, 2H), 1.91–1.61 (m, 6H); MS (ESI): m/z 308.4 [M + H+].

11-(p-Tolyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-2

68 %; yellow solid, mp: 120–123 oC; 13C NMR: δ 148.01, 139.1, 138.2, 136.2, 135.9, 133.4, 129.6, 126.1, 123.5, 108.2, 106.5, 66.3, 30.2, 26.7, 23.2, 22.7, 21.2; 1H NMR: δ 7.24–7.11 (m, 4H), 6.87 (t, 1H, J = 7.8), 6.73–6.65 (m, 2H), 5.96 (t, 1H, J = 6.6), 5.32 (s, 1H), 2.32– 2.30 (m, 5H), 1.79–1.58 (m, 6H); MS (ESI): m/z 276.2 [M + H+]

11-(4-Methoxyphenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-3

65 %; cream solid, mp: 83–88 oC; 13C NMR: δ 159.7, 148.9, 136.6, 135.4, 135.1, 133.4, 128.3,123.5, 114.2, 108.6, 107.0, 67.9, 55.3, 30.2, 26.7, 23.2, 22.8; 1H NMR: δ 7.27–7.21 (m, 2H), 6.88–6.84 (m, 3H), 6.76–6.68 (m, 2H), 5.99 (t, 1H, J = 6.6), 5.32 (s, 1H), 3.79 (s, 3H), 2.39–2.29 (m, 2H), 1.77–1.57 (m, 6H); MS (ESI): m/z 293.56 [M+ H+].

11-(4-fluorophenyl)-2, 3, 4, 11-tetrahydro-IH-pyrido [2, 1-b] quinazoline-4

70 %; pale yellow solid, mp: 88–90 0C; 13C NMR: δ 148.8, 141.9, 137.5, 135.2, 134.5, 133.0, 129.4, 128.3, 123.6, 108.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; 1H NMR: δ 7.50–7.21 (m, 7H),6.62 (t, 1H, J = 6.0), 5.64 (s, 1H), 2.47–2.36 (m, 2H), 1.88–1.61 (m, 6H); MS (ESI): m/z 297.9 [M + H+].

11-(4-Nitrophenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b]quinazoline-5

75 %; yellow solid, mp: 148–152 oC; 1H NMR: δ 8.20–8.22 (m, 2H), 7.44–7.35 (m, 3H), 7.34–7.20 (m, 1H), 7.07 (d, 1H, J = 6.3), 6.36 (t, 1H, J = 6.3), 5.62 (s, 1H), 2.53–2.37 (m, 2H), 1.91–1.61 (m, 6H); MS (ESI): m/z 308.6 [M + H+].

11-(3-Chlorophenyl)-2, 3, 4, 11-tetrahydro-IH-pyrido [2, 1-b] quinazoline-6

78 %; brown solid, mp: 86–89 0C; 1H NMR: δ 7.40–7.31 (m, 7H), 6.52 (t, 1H, J = 6.0), 5.64 (s, 1H), 2.37–2.36 (m, 2H), 1.88–1.61 (m, 6H); 13C NMR: δ 148.8, 141.9, 137.5, 135.2,134.5, 133.0, 129.4, 128.3, 123.6, 108.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; MS (ESI): m/z297.88 [M + H+].

11-(3-Chlorophenyl)-2, 3, 4, 11-tetrahydro-IH-pyrido [2, 1-b] quinazoline-7

65%; yellow solid, mp: 80–83 0C; 1H NMR: δ 7.55–7.21 (m, 7H), 6.67 (t, 1H, J = 6.0), 5.54 (s, 1H), 2.47–2.36 (m, 2H), 1.88–1.61 (m, 6H); 13C NMR: δ 148.8, 141.9, 137.5, 135.2, 134.5, 133.0, 129.4, 128.3, 123.6, 108.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; MS (ESI): m/z 297.7 [M + H+].

8-Chloro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] Quinazoline-8

76 %; light solid, mp: 129–133 oC; 13C NMR: δ 146.8, 140.4, 136.6, 134.9,134.8, 132.5,129.4, 128.3, 124.6, 115.3, 107.4, 68.0, 29.9, 26.6, 22.9, 22.5; 1H NMR: δ 7.35–7.32 (m, 2H), 7.27–7.22 (m, 2H), 6.89–6.85 (m, 1H), 6.78 (s, 1H), 6.75 (d, 1H, J = 2.1), 5.32 (s, 1H), 2.34– 2.23 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 330.3 [M + H+].

8-Chloro-11-(3-nitrophenyl)-2,3,4,11-tetrahydro-1H-pyrido[2,1-b] quinazoline -11

80 %; cream solid, mp: 120–122 oC; 13C NMR: δ 143.8, 140.4, 136.6, 135.9,133.8, 132.5, 129.4, 128.3, 122.6, 115.3, 107.4, 68.0, 29.9, 26.6, 22.9, 22.5; 1H NMR: δ 7.32–7.26 (m, 2H),7.27–7.22 (m, 2H), 6.89–6.75 (m, 1H), 6.78 (s, 1H), 6.75 (d, 1H, J = 2.1), 5.32 (s, 1H), 2.34– 2.23 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 330.4[M + H+].

phenyl)-2, 3, 4,Chloro 11-tetrahydro-IH-pyrido [2, 1-b] quinazoline-12

82 %; white solid, mp: 80–83 0C; 13C NMR: δ 147.8, 142.9, 137.5, 134.2, 133.5, 131.0, 129.4, 128.3, 123.6, 105.3, 106.8, 67.8, 29.6, 26.4, 23.0, 22.6; 1H NMR: δ 7.40–7.21 (m, 7H), 6.52 (t, 1H, J = 6.0), 5.44 (s, 1H), 2.47–2.36 (m, 2H), 1.88–1.61 (m, 6H); MS (ESI): m/z 296.9 [M + H+].

8-Fluoro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] Quinazoline-13

76 %; white solid, mp: 127–130 oC; 13C NMR: δ 143.8, 136.4, 131.6, 125.9,124.8, 122.5, 119.4, 118.3, 114.6, 105.3, 104.4, 68.0, 29.9, 26.6, 22.9, 22.5; 1H NMR: δ 7.25–7.12 (m, 2H), 7.27–7.22 (m, 2H), 6.49–6.85 (m, 1H), 6.18 (s, 1H), 6.75 (d, 1H, J = 2.1), 5.32 (s, 1H), 2.34– 4522.23 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 329.27 [M + H+].

8-Nitro-11-(4-chlorophenyl)-2, 3, 4, 11-tetrahydro-1H-pyrido [2, 1-b] Quinazoline-14

72 %; yellow solid, mp: 129–135 oC; 13C NMR: δ 146.8, 140.4, 136.6, 134.9,134.8, 132.5,129.4, 128.3, 124.6, 115.3, 107.4, 68.0, 29.9, 26.6, 22.9, 22.5; 1H NMR: δ 7.45–7.42 (m, 2H),17.37–7.22 (m, 2H), 6.89–6.75 (m, 1H), 6.68 (s, 1H), 6.45 (d, 1H, J = 2.1), 5.12 (s, 1H), 2.34–2.13 (m, 2H), 1.77–1.59 (m, 6H); MS (ESI): m/z 329.8 [M + H+].

Conclusion:

In summery we developed of 4H-prido-[1,2-] pyramidine derivates from the 2- aminopyrimidines, aldehydes and ketones by using recyclable and reusable catalyst it under go one pot the component system to formation of 4H-prido-[1,2-] pyramidine compounds these are good to excellent yields and it is the more efficient and simple method for scope of organic chemistry synthesis.

Materials and methods:

All chemicals and reagents were obtained from Aldrich Lancaster (Alfa Aeser, Johnson Matthey Company, Ward Hill, MA, USA), or Spectrochem Pvt. Ltd. (Mumbai, India) and were used without further purification. Reactions were performer by TLC performed on silica gel glass plate containing 60 GF-254, and visualization was achieved by UV light or iodine indicator. 1H and 13C NMR spectra were determined in CDCl3 by using Varian and Avance instruments. Chemical shifts are expressed in parts per million (� in ppm) downfield from internal TMS and coupling constants are expressed in Hz. 1H NMR spectroscopic data coupling constants in Hz, number of protons. ESI mass spectra were recorded on a Micro mass Quattro LC using ESI+ software with capillary voltage 3.98 kV and an ESI mode positive ion trap detector. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected.

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Reference:

1. E. Badawey, S.M. Rida, A.A. Hazza, H.T.Y. Fahmy, Y.M. Gohar, Potential antimicrobials.II. Synthesis and in vitro anti-microbial evaluation of some thiazolo[4,5-d]pyrimidines, Eur. J. Med. Chem. 28 (1993) 97e101.

2. E. Badawey, S.M. Rida, A.A. Hazza, H.T.Y. Fahmy, Y.M. Gohar, Potential antimicrobials.I. Synthesis and structure-activity studies of some new thiazolo [4,5- d]pyrimidine derivatives, Eur. J. Med. Chem. 28 (1993) 91e96

3. S.M. Rida, N.S. Habib, E.A. Badawey, H.T. Fahmy, H.A. Ghozlan, Synthesis of novel thiazolo[4,5-d]pyrimidine derivatives for antimicrobial, anti-HIV and anticancer investigation, Die Pharm. 51 (1996) 927e931.

4. H.T. Fahmy, S.A. Rostom, M.N. Saudi, J.K. Zjawiony, D.J. Robins, Synthesis and in vitro evaluation of the anticancer activity of novel fluorinated thiazolo[4, 5- d]pyrimidines, Arch. Pharm. 336 (2003) 216e225.

5. A.A. Bekhit, H.T. Fahmy, S.A. Rostom, A.M. Baraka, Design and synthesis of some substituted 1H-pyrazolyl-thiazolo[4,5-d]pyrimidines as antiinflammatory- antimicrobial agents, Eur. J. Med. Chem. 38 (2003) 27e36.

6. (a) Domling, A. Chem. Rev. 2006, 106, 17–89; (b) Banfi, L.; Riva, R. Org. React. 2005, 65, 1–140; (c) Ramo´ n, D. J.; Yus, M. Angew. Chem. 2005, 117, 1628–1661. Angew. Chem., Int. Ed. 2005, 44, 1602–1634; (d) Zhu, J. Eur. J. Org. Chem. 2003, 1133–1144.

7. (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Acc. Chem. Res. 1996, 29, 123–131; (b) Schreiber, S. L. Science 2000, 287, 1964– 1969; (c) Werner, S.; Turner, D. M.; Lyon, M. A.; Huryn, D. M.; Wipf, P. Synlett 2006, 2334–2338. and references cited therein.

8. (a) Inanaga, K.; Takasu, K.; Ihara, M. J. Am. Chem. Soc. 2004, 126, 1352–1353; (b) Powell, D. A.; Batey, R. A. Org. Lett. 2002, 4, 2913–2916.

9. (a) Marques, M. M. B. Angew. Chem. 2006, 118, 356–360. Angew. Chem., Int. Ed. 2006, 45, 348–352; (b) Co´ rdova, A. Acc. Chem. Res. 2004, 37, 102–112.

10. (a) Domling, A.; Ugi, I. Angew. Chem. 2000, 112, 3300–3344. Angew. Chem., Int. Ed. 2000, 39, 168–3210; For recent studies, see: (b) Giovenzana, G. B.; Tron, G. C.; Paola, S. Di; Menegotto, I. G.; Pirali, T. Angew. Chem. 2006, 118, 1117–1120. Angew. Chem., Int. Ed. 2006, 45, 1099–1102; (c) Kaim, L. El.; Grimaud, L.; Oble, J. Angew. Chem. 2005, 117, 8175–8178. Angew. Chem., Int. Ed. 2005, 44, 7961–7964;

(d) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. Org. Lett. 2006, 8, 4351–4354.

11. Movassaghi, M.; Jacobsen, E. N. Science 2002, 298, 1904–1905; Hongming, Li.; Wang, B.; Deng, Li. J. Am. Chem. Soc. 2006, 128, 732–733.

12. (a) Kappe, C. O. Acc. Chem. Res. 2000, 33, 879–888; (b) Kappe, C. O. QSAR Comb. Sci. 2003, 22, 630–645; For recent research, see: (c) Nilsson, B. L.; Overman, L. E. J Org. Chem. 2006, 71, 7706–7714; (d) Cohen, F.; Overman, L. E. J. Am. Chem. Soc. 2006, 128, 2604–2608; (e) Suzuki, I.; Suzumura, Y.; Takeda, K. Tetrahedron Lett. 2006, 47, 7861–7864; (f) Debache, A.; Boumoud, B.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. Tetrahedron Lett. 2006, 47, 5697–5699; (g) Huang, Y.; Yang, F.; Zhu, C. J. Am. Chem. Soc. 2005, 127, 16386–16387.

13. Kumar, A.; Maurya, R. A. Tetrahedron 2007, 63, 1946–1952.

14. (a) Bogevig, A.; Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Jorgensen, K. A. Angew. Chem., Int. Ed. 2002, 41, 1790–1793; (b) Janey, J. M.; Hsiano, Y.; Armstrong, J. D., III J. Org. Chem. 2006, 71, 390–392.

15. (a) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. J. Am. Chem. Soc. 2002, 124, 827–833; (b) Kotrusz, P.; Toma, S. Molecules 2006, 11, 197–205. For recent reviews, see: (a) Domling, A. Chem. Rev. 2006, 106, 17– 89. (b) Banfi, L.; Riva, R. Org. React. 2005, 65, 1–140. (c) Ramón, D. J.; Yus, M. Angew. Chem. 2005, 117, 1628–1661; Angew. Chem., Int. Ed. 2005, 44, 1602– 1634. (d) Zhu, J. Eur. J. Org. Chem. 2003, 1133–1144.

16. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Acc. Chem. Res. 1996, 29, 123–131.

17. Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. J. Am. Chem. Soc. 2002, 124, 6552–6554.

18. Leoni, L. M.; Hamel, E.; Genini, D.; Shih, H.; Carrera, C. J.; Cottam, H. B.; Carson, D. A. J. Natl. Cancer Inst. 2000, 92, 217.

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