Silica-Supported Perchloric Acid ($HClO_4$–SiO_2): An Efficient Catalyst for One-Pot Synthesis of Functionalized Tetrahydropyrimidine Derivatives

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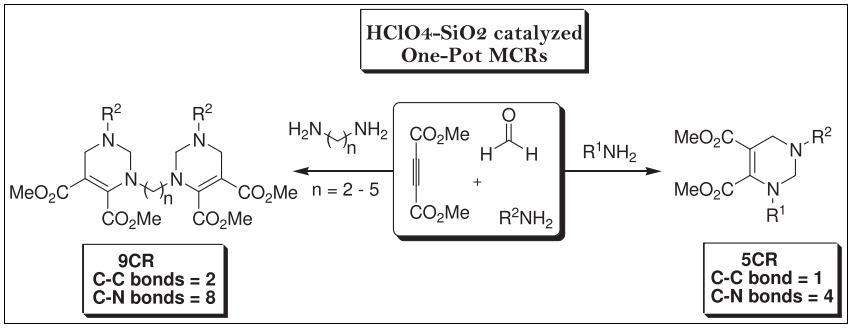

$HClO_4$–SiO_2 has been found to be a highly efficient catalyst for the synthesis of substituted tetrahydropyrimidine and bis-tertahydropyrimidine derivatives in good to excellent yields involving the reaction of dimethyl acetylenedicarboxylate, amines/diamines, and formaldehyde. One-pot, atom economy, high-bond forming efficiency, environmentally benign, good yields, and mild reaction conditions are some of the salient features of this multicomponent reaction.

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INTRODUCTION

In recent times, multicomponent reactions (MCRs) have emerged as an important and promising tool in organic chemistry for construction of architecturally complex molecules [1,2]. These reactions have been explored in the total syntheses of natural products and synthetic building blocks [2,3]. They avoid time-consuming, expensive processes for purification of various precursors as well as cumbersome steps of protection and deprotection of functional groups. In addition, these reactions are environmentally benign and often proceed with excellent chemoselectivities [4]. Hence, MCRs are considered as a new type of "Green Chemistry." To devise a new selective cascade, reaction is a challenging task at the forefront of organic chemistry so the interest in MCRs is increasing gradually. Of late, the authors have developed various synthetic methodologies using MCR approach to synthesize new entities leading to chemical and pharmaceutical interest [5].

Pyrimidine and its analogs are important class of nitrogen heterocyclic pharmacophores, which are present in many pharmaceuticals. Some of them are in clinical and preclinical trial stage and also exhibits interesting biological activities [6] such as muscarinic agonist activity [7], antiviral activity [8], anti-inflammatory activity [9], and protein–nucleic acid interactions [10]. Pyrimidine skeleton is a key structural motif found in various naturally occurring compounds [11] and they also serve as building block for various organic synthesis [12]. Owing to the importance of tetrahydropyrimidine derivatives, a considerable attention has been paid to the synthesis of these compounds over the years [13,14]. These methods are associated with certain limitations such as use of expensive and excess amount of catalyst, long reaction times and drastic reaction conditions. In addition, the synthesis of bis-tetrahydropyrimidine derivatives using MCRs has not yet been reported. Therefore, there is a need to develop a synthetic methodology using a catalyst, which might work under milder reaction conditions.

$HClO_4$–SiO_2 is an inexpensive, nontoxic, reusable, environmentally benign as well as highly efficient catalyst and it has been utilized for various organic transformations [15]. The usefulness of this catalyst has been demonstrated by the authors for geminal diacylation of aldehydes [16a], tetrahydropyranylation, oxathioacetalization and thioacetylation [16b], and aza-Michael reaction [16c]. The efficiency of $HClO_4$–SiO_2 was shown in other one-pot MCRs [17] and its advantage is going to be explored further. In this article, the authors have reported the synthesis of substituted tetrahydropyrimidine and bis-tetrahydropyramidine derivatives using $HClO_4$–SiO_2 as a heterogeneous catalyst (Scheme 1).

RESULTS AND DISCUSSION

For the present study, the catalyst $HClO_4$–SiO_2 was prepared by following the published reports procedure [17].

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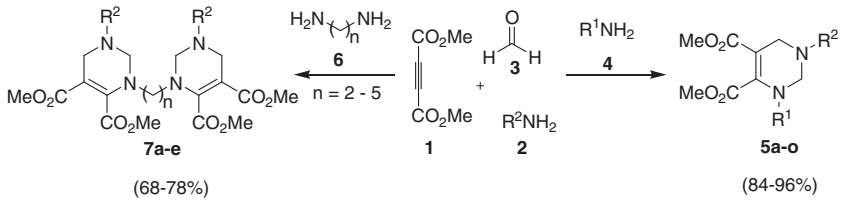
Scheme 1. Synthesis of tetrahydropyrimidine derivatives.



The reaction of dimethyl acetylenedicarboxylate (DMAD, **1**), aniline (**2a**), and formaldehyde (**3**) using $HClO_4$–SiO_2 as a catalyst at room temperature was examined and it smoothly converted into the functionalized tetrahydropyrimidine derivative **5a** within 1.5 h giving 95% yield.

The reaction conditions were optimized by varying the amount of catalyst and stoichiometric ratios of the reactants (DMAD, aniline, and formaldehyde) to obtain best result in terms of reaction time and yield (Table 1, entries 1–4). The optimized amount of catalyst ($HClO_4$–SiO_2) was determined to be 25 mg (0.125 mmol). The optimal amount of the reactants such as DMAD (**1**), aniline (**2a**), and formaldehyde (**3**) was found to be 1.0, 2.0, and 2.5 equiv, respectively. Various solvents namely MeCN, DMF, DCM, MeOH, EtOH, and H_2O were also screened and MeOH was found to be the best solvent among them (Table 1, entries 4–9).

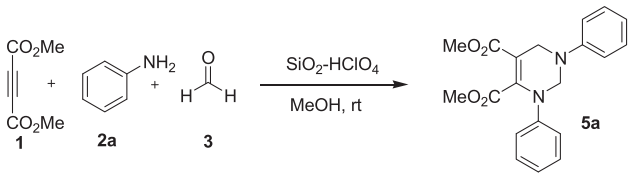
The reaction was performed without the catalyst in methanol at room temperature, which gave only 52% yield after 5 h (Table 1, entry 10). In the case of neat reaction, the product **5a** was obtained in 55% yield using the same amount of catalyst. These results indicate that the catalyst and solvent have definite role in the reaction both in terms of time and yield. This might be due to lack of proper interaction between the reactants (Table 1, entry 11).

After optimization of the reaction conditions, the reaction of 4-methylaniline (2 mmol) with DMAD (1 mmol), formaldehyde (2.5 mmol) using $HClO_4$–SiO_2 (25 mg, 2.5 mol %) in methanol was performed. The product **5b** was obtained in 96% yield. The scope of this protocol was investigated using the same reaction condition for substituted anilines. Me, Et, MeO, Cl, and Br were the substituents that was used in these studies. The desired products **5c–i** were obtained in good to excellent yields.

The present method was also tested with aliphatic amines namely *n*-butylamine, benzylamine, furfurylamine, and cyclohexylamine under identical reaction conditions to furnish tetrahydropyrimidines **5j–m** in good yields (Table 2, entries 10–13). It is observed that the aliphatic amines require shorter reaction time than the aromatic amines.

Table 1

Screening of reaction conditions for the synthesis of tetrahydropyrimidine **5a**.

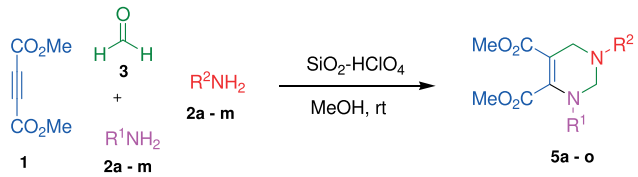


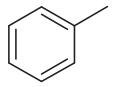
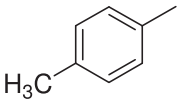
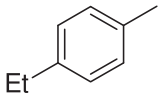
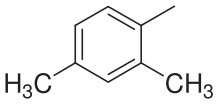
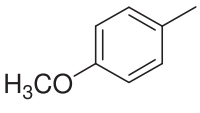
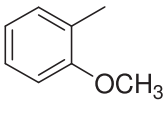
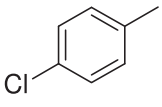
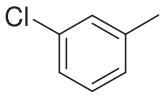
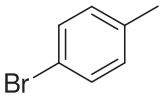
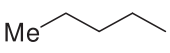
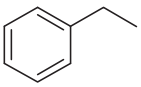
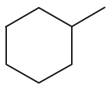
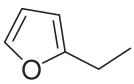
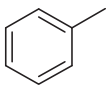
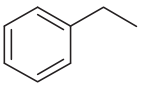
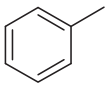
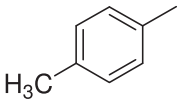
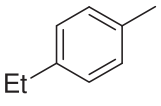
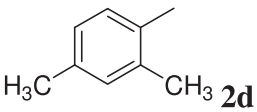
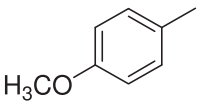
Entry	Solvent	Amount of Catalyst (in mg)	Molar ratio (1:2:3)	Time (h)	Yield[a] (%)
1	CH_3OH	25	1:2:4	1.5	95
2	CH_3OH	50	1:2:4	1.5	94
3	CH_3OH	25	1:2:3	1.5	95
4[b]	**CH_3OH**[b]	**25**[b]	**1:2:2.5**[b]	**1.5**[b]	**95**[b]
5	CH_3CN	25	1:2:3	2	88
6	DMF	25	1:2:3	2.5	88
7	DCM	25	1:2:3	2	76
8	EtOH	25	1:2:3	1.5	89
9	H_2O	25	1:2:3	2	72
10	CH_3OH	No catalyst	1:2:4	5	52
11	No solvent	25	1:2:3	5	55

[a]Isolated yield.
[b]The experimental condition is the best optimized condition for obtaining the product.

Table 2

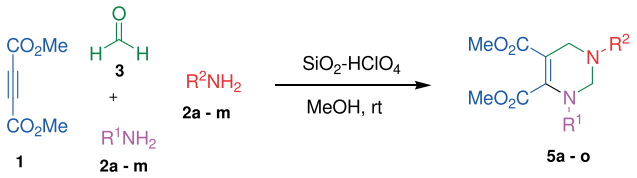
Scope of the one-pot synthesis of tetrahydropyrimidines **5** catalyzed by $HClO_4$–SiO_2.

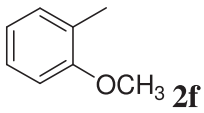
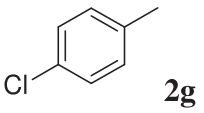
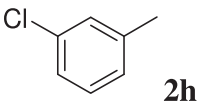
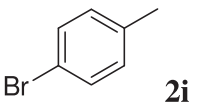
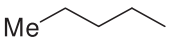
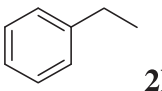
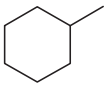
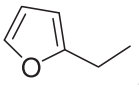
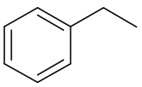
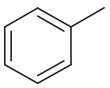


Entry	R^1	R^2	Time (h)	Product	Yield[a] (%)
1	 **2a**	 **2b**	1.5	**5a**	95
2	 **2c**	 **2d**	1.5	**5b**	96
3	 **2e**	 **2f**	1.5	**5c**	92
4	 **2g**	 **2h**	2.5	**5d**	91
5	 **2i**	 **2j**	1.5	**5e**	92
6	 **2k**	 **2l**	2.0	**5f**	84
7	 **2m**	 **2a**	2.0	**5g**	94
8	 **2k**	 **2a**	2.0	**5h**	88
9	 **2b**	 **2c**	2.0	**5i**	93
10	 **2d**	 **2e**	1.0	**5j**	95

(*Continues*)

Table 2. *(Continued)*



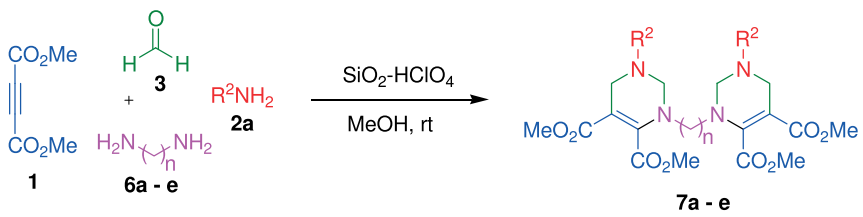
Entry	R^1	R^2	Time (h)	Product	Yield[a] (%)
11	 **2f**	 **2g**	1.0	**5k**	92
12	 **2h**	 **2i**	1.0	**5l**	96
13	 **2j**	 **2k**	1.5	**5m**	91
14	 **2l**	 **2m**	2	**5n**	86
15	 **2k**	 **2a**	2	**5o**	88

[a]Isolated yield.

The substituent pattern of the pyrimidine ring at positions 1 and 3 can be altered by changing the sequence of addition of the amines. The product **5n** was obtained when aniline (**2a**) was added with DMAD followed by the addition of benzylamine (**2k**) and formaldehyde (**3**), while the product **5o** was isolated by changing the order of the

Table 3

Scope of the one-pot domino reaction for the synthesis of bis-tetrahydropyrimidines.



Entry	n	Time (h)	Product	Yield[a] (%)
1	2, **6a**	2	**7a**	74
2	3, **6b**	2	**7b**	71
3	4, **6c**	2	**7c**	76
4	5, **6d**	2	**7d**	68
5	6, **6e**	2	**7e**	78

[a]Isolated yields.

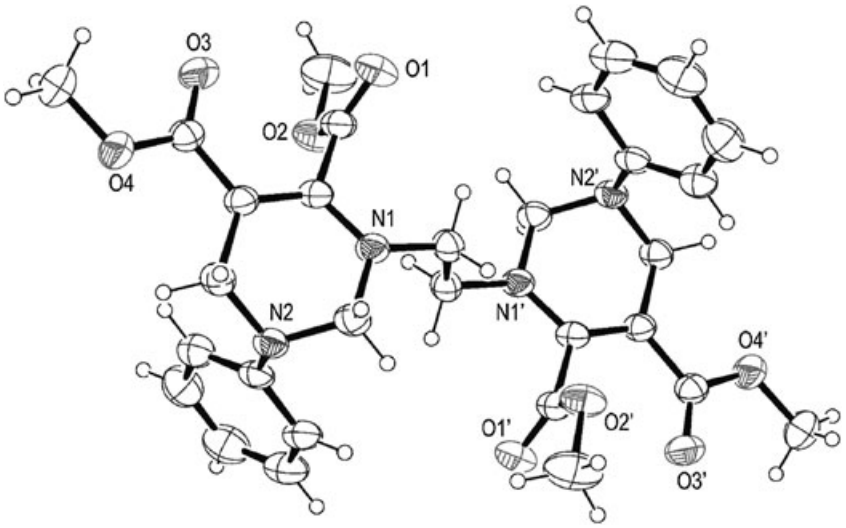


Figure 1. X-ray crystal structure of **7a** (CCDC no. 756205).

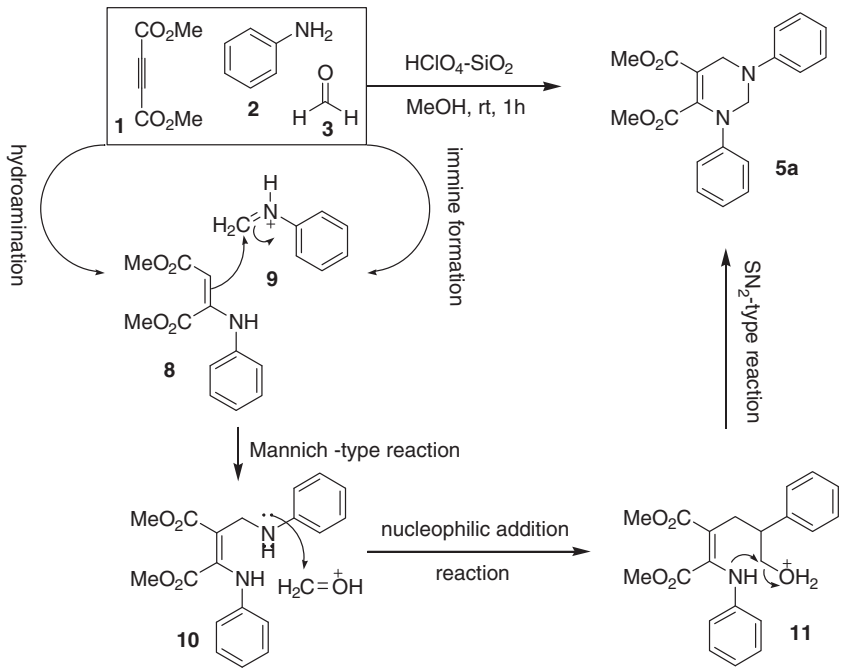
amines that is benzylamine was added first followed by aniline.

The synthetic utility of the present protocol was further extended by synthesizing bis-pyrimidine derivatives. The reaction of DMAD (**1**, 2 mmol) with ethylenediamine (**6a**, 1 mmol), followed by addition of aniline (**2a**, 2 mmol) and formaldehyde (5 mmol) using $HClO_4$–SiO_2 (50 mg, 5 mol %) as a catalyst provides a bis-tetrahydropyrimidine derivative **7a** (Table 3, entry 1). The product **7a** was fully characterized by ^1H and ^{13}C NMR spectra as well as elemental analysis. The structure of compound **7a** was confirmed by single X-ray crystallographic data. The tetrahydropyrimidine ring adopted envelope conformation and the orientation of two rings are found to be anti to each other as shown in Figure 1.

The reaction of other aliphatic diamines such as 1,3-diamine (**6b**), 1,4-diamine (**6c**), 1,5-diamine (**6d**), and 1,6-diamine (**6e**) were examined individually with DMAD (**1**), aniline (**2a**), and formaldehyde (**3**) under the same experimental conditions and the results are summarized in Table 3.

A plausible mechanism for the formation of tetrahydropyrimidine **5a** involves the initial formation of hydroamination

Scheme 2. Plausible mechanism for the formation of tetrahydropyrimidine.



product **8**, which reacts with acid protonated imine **9** to form intermediate **10** via Mannich-type reaction. The intermediate **10** reacts with acid protonated formaldehyde to give species **11** by nucleophilic addition reaction. Finally, the intermediate **11** undergoes intramolecular SN_2 type reaction to furnish the desired product **5a** via elimination of a water molecule as shown in Scheme 2. All the products **5a–o** and **7a–e** were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra, and by elemental analysis.

CONCLUSION

In conclusion, the efficacy and generality of $HClO_4$–SiO_2 as a versatile catalyst for the synthesis of tetrahydropyrimidines using DMAD, amines, and formaldehyde have been demonstrated. In addition, the synthesis of novel bis-tetrahydropyrimidine derivatives has been achieved using aliphatic diamines under the same experimental conditions. The salient features of this protocol are good yields, mild reaction conditions, superior atom economy, environmentally benign, easy accessibility of the catalyst, and its cost effectiveness. These pyrimidine derivatives can be used for other organic transformation and these reactions are under progress.

EXPERIMENTAL

Melting points were determined on a Büchi-melting point apparatus. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer using TMS internal standard; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR spectra are reported in the order: multiplicity, coupling constant (J value) in hertz (Hz), and no of protons. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K.

General procedure for the synthesis of tetrahydropyrimidine derivatives 5. A mixture of DMAD (1 mmol) and amines (2 mmol) in MeOH (3 mL) was stirred at room teperatutre for 10 min. Then 38% formaldehyde solution (200 mg, 2.5 mmol) in methanol (2 mL) and the catalyst $HClO_4$–SiO_2 (25 mg, 1.25 mol%) were added successively into the reaction vessel. After completion of reaction as monitored by TLC, methanol was removed and the crude residue was extracted with dichloromethane (2 × 20 mL). The organic layer was washed with $NaHCO_3$ solution, brine, and finally with water. The solvent was removed and crude material was purified by column chromatography using ethyl acetate/hexane (1:9) as eluent to give the pure products **5a–o**.

Compound 5a. Yellow liquid (334 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (s, 3 H), 3.74 (s, 3 H), 4.27 (s, 2 H), 4.92 (s, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 7.16–7.29 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.7, 51.7, 52.6, 69.0, 100.7, 118.0, 121.3, 125.2, 126.6, 129.4, 143.8, 146.7, 148.4, 164.7, 166.3; IR (KBr): 2950, 1743, 1697, 1580, 1495, 1261, 1112 cm^{-1}; Anal. Calcd for $C_{20}H_{20}N_2O_4$ (352.39): C, 68.17; H, 5.72; N, 7.95; Found: C, 68.01; H, 5.61; N, 7.73.

Compound 5b. Yellow liquid (365 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.30 (s, 3 H), 3.58 (s, 3 H), 3.72 (s, 3 H), 4.22 (s, 2 H), 4.85 (s, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 21.0, 47.6, 51.4, 52.4, 69.2, 98.9, 118.1, 125.1, 129.8, 129.9, 130.6, 136.4, 140.9, 146.0, 147.0, 164.6, 166.2; IR (KBr): 2949, 2863, 1742, 1698, 1588, 1514, 1434, 1259, 1112 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.54; H, 6.23; N, 7.12.

Compound 5c. Semi solid (376 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 0 (t, *J* = 7.6 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 2.53–2.63 (m, 4 H), 3.58 (s, 3 H), 3.73 (s, 3 H), 4.23 (s, 2 H), 4.86 (s, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 15.9, 28.1, 28.5, 47.8, 51.6, 52.6, 69.3, 99.2, 118.3, 125.3, 128.7, 128.8, 137.3, 141.1, 142.8, 146.3, 147.1, 164.8, 166.4; IR (KBr): 2963, 2872, 1744, 1697, 1588, 1514, 1434, 1260, 1110 cm^{-1}; Anal. Calcd for $C_{24}H_{28}N_2O_4$ (408.50): C, 70.57; H, 6.91; N, 6.86. Found: C, 70.51; H, 6.80; N, 6.66.

Compound 5d. Yellow liquid (378 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 2.27 (s, 3 H), 3.52 (s, 3 H), 3.71 (s, 3 H), 4.04 (s, 2 H), 4.32 (d, *J* = 11.6 Hz, 1 H), 4.49 (d, *J* = 11.6 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 18.1, 20.9, 21.1, 48.8, 51.4, 52.4, 69.8, 96.9, 121.4, 127.1, 127.3, 128.8, 131.7, 132.0, 137.7, 133.9, 136.4, 138.0, 138.8, 146.0, 148.4, 164.9, 166.5; IR (KBr): 2950, 2859, 1744, 1697, 1592, 1502, 1435, 1263, 1111 cm^{-1}; Anal. Calcd for $C_{24}H_{28}N_2O_4$ (408.50): C, 70.57; H, 6.91; N, 6.86. Found: C, 70.43; H, 6.79; N, 6.71.

Compound 5e. Yellow liquid (379 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 3 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.18 (s, 2 H), 4.77 (s, 2 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 9.2 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.9, 51.5, 52.6, 55.5, 55.7, 70.8, 97.5, 114.4, 114.6, 120.5, 127.5, 136.2, 142.4, 147.7, 154.9, 158.4, 164.7, 166.4; IR (KBr): 2950, 2837, 1742, 1694, 1579, 1511, 1435, 1247, 1110 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.45): C, 64.07; H, 5.87; N, 6.79. Found: C, 63.96; H, 5.72; N, 6.48.

Compound 5f. Yellow liquid (346 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 4.21 (s, 2 H), 4.80 (br s, 2 H), 6.67–6.71 (m, 2 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 7.12 (td, *J* = 7.2 Hz, *J* = 2.4 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.0, 51.4, 52.4, 55.5, 55.9, 68.4, 97.4, 111.3, 111.9, 120.4, 120.8, 121.0, 124.0, 128.5, 128.52, 131.7, 137.9, 147.8, 152.2, 155.4, 164.6, 166.4; IR (KBr): 2949, 2838, 1743, 1693, 1581, 1501, 1436, 1264, 1108 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_6$ (412.45): C, 64.07; H, 5.87; N, 6.79. Found: C, 64.01; H, 5.71; N, 6.63.

Compound 5g. Light yellow solid (396 mg, 94%); mp 128–130° C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (s, 3 H), 3.75 (s, 3 H), 4.23 (s, 2 H), 4.85 (s, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6, 51.9, 52.9, 69.1, 101.6, 119.3, 126.2, 126.5, 129.4, 129.7, 132.3, 142.2, 146.1, 146.7, 164.4, 165.9; IR (KBr): 2953, 1744, 1688, 1571, 1491,

1266, 1228, 1117 cm^{-1}; Anal. Calcd for $C_{20}H_{18}N_2O_4Cl_2$ (421.28): C, 57.02; H, 4.30; N, 6.65. Found: C, 56.91; H, 4.19; N, 6.42.

Compound 5h. Yellow liquid (371 mg, 88%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3 H), 3.76 (s, 3 H), 4.23 (s, 2 H), 4.87 (s, 2 H), 6.72 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H), 6.83 (t, *J* = 2.0 Hz, 1 H), 6.86 (dq, *J* = 8.0 Hz, *J* = 0.8 Hz, 1 H), 6.90 (dq, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 7.04 (t, *J* = 2.4 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.17 (m, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.7, 52.0, 52.9, 68.2, 103.4, 115.5, 117.7, 121.3, 122.6, 124.7, 126.7, 130.5, 130.6, 135.2, 135.3, 144.9, 145.6, 149.2, 164.5, 165.9; IR (KBr): 2950, 2843, 1742, 1703, 1591, 1482, 1262, 1114 cm^{-1}; Anal. Calcd for $C_{20}H_{18}N_2O_4Cl_2$ (421.28): C, 57.02; H, 4.30; N, 6.65. Found: C, 56.98; H, 4.17; N, 6.50.

Compound 5i. Light yellow solid (474 mg, 93%); mp 150–152°C; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.62 (s, 3 H), 3.75 (s, 3 H), 4.22 (s, 2 H), 4.85 (s, 2 H), 6.75 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6, 51.8, 52.9, 68.8, 101.8, 113.7, 119.5, 120.1, 126.3, 132.3, 132.6, 142.7, 145.9, 147.2, 164.4, 165.9; IR (KBr): 2951, 1744, 1689, 1591, 1568, 1487, 1265, 1227, 1116 cm^{-1}; Anal. Calcd for $C_{20}H_{18}N_2O_4Br_2$ (510.20): C, 47.08; H, 3.56; N, 5.49. Found: C, 47.01; H, 3.42; N, 5.29.

Compound 5j. Yellow liquid (297 mg, 95%); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H), 1.24–1.32 (m, 2 H), 1.34–1.41 (m, 2 H), 1.47–1.56 (m, 4 H), 2.53 (t, *J* = 7.6 Hz, 2 H), 3.01 (t, *J* = 7.6 Hz, 2 H), 3.50 (s, 2 H), 3.64 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.2, 20.0, 20.6, 30.3, 31.4, 48.2, 51.0, 52.6, 52.8, 67.7, 91.1, 148.4, 165.6, 167.1; IR (KBr): 2956, 2870, 1743, 1689, 1582, 1434, 1285, 1249, 1145 cm^{-1}; Anal. Calcd for $C_{16}H_{28}N_2O_4$ (312.41): C, 61.51; H, 9.03; N, 8.97. Found: C, 61.51; H, 8.92; N, 8.81.

Compound 5k. Yellow liquid (350 mg, 92%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.55 (s, 2 H), 3.60 (s, 2 H), 3.65 (s, 3 H), 3.84 (s, 2 H), 3.91 (s, 3 H), 4.16 (s, 2 H), 7.15–7.18 (m, 2 H), 7.22–7.32 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.4, 51.3, 53.1, 54.4, 57.1, 66.1, 92.2, 127.4, 128.2, 128.24, 128.5, 128.9, 136.3, 138.1, 148.4, 165.8, 167.1; IR (KBr): 2949, 2855, 1740, 1689, 1582, 1434, 1286, 1110 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.45): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.39; H, 6.25; N, 7.18.

Compound 5l. Yellow liquid (350 mg, 96%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.3 (m, 8 H), 1.35–1.45 (m, 2 H), 1.62–1.92 (m, 10 H), 2.43–2.52 (m, 1 H), 2.97 (tt, *J* = 11.6 Hz, *J* = 4.8 Hz, 1H), 3.54 (s, 2 H), 3.64 (s, 3 H), 3.90 (s, 3 H), 4.01 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 25.6, 25.9, 26.1, 30.5, 31.4, 45.5, 51.0, 52.8, 59.0, 60.0, 60.2, 92.7, 149.0, 166.0, 166.8; IR (KBr): 2932, 1742, 1688, 1582, 1435, 1287, 1239, 1117 cm^{-1}; Anal. Calcd for $C_{20}H_{32}N_2O_4$ (364.49): C, 65.91; H, 8.85; N, 7.69. Found: C, 65.79; H, 8.75; N, 7.53.

Compound 5m. Yellow liquid (328 mg, 91%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.59 (s, 2 H), 3.63 (s, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 4.05 (s, 2 H), 4.19 (s, 2 H), 6.13 (d, *J* = 3.2 Hz, 1 H), 6.26 (d, *J* = 3.2 Hz, 1 H), 6.30 (d, *J* = 3.0 Hz, 1 H), 6.33 (d, *J* = 3.0 Hz, 1 H), 7.37–7.38 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.9, 47.8, 49.2, 51.3, 66.3, 92.5, 109.2, 110.3, 110.8, 142.7, 143.0, 149.9, 151.5, 165.3, 166.9; IR (KBr): 2951, 1739, 1688, 1582, 1435, 1284, 1247, 1188, 1109 cm^{-1}; Anal. Calcd for $C_{18}H_{20}N_2O_6$ (360.37): C, 59.99; H, 5.59; N, 7.77. Found: C, 59.91; H, 5.48; N, 7.61.

Compound 5n. Yellow liquid (315 mg, 86%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 3 H), 3.67 (s, 3 H), 3.71 (s, 2 H), 3.81 (s, 2 H), 4.36 (s, 2 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.24 (br s, 5 H), 7.30 (t, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.8, 51.4, 52.6, 56.7, 69.8, 97.3, 124.8, 126.3, 127.5, 128.4, 129.0, 129.3, 137.8 143.7, 145.9, 164.8, 166.8; IR (KBr): 2951, 2860, 1739, 1688, 1582, 1284, 1247, 1109 cm^{-1}; Anal. Calcd for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.72; H, 5.91; N, 7.49.

Compound 5o. Yellow liquid (322 mg, 88%); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 3.85 (s, 3 H), 4.12 (s, 2 H), 4.21 (s, 2 H), 4.42 (s, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.90 (t, *J* = 7.6 Hz, 1 H), 7.17–7.24 (m, 4 H), 7.26–7.31 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.4, 51.4, 53.0, 54.5, 65.4, 94.8, 117.8, 121.2, 128.0, 128.1, 128.8, 129.3, 135.8, 148.4, 149.0, 165.5, 166.4; IR (KBr): 2963, 2872, 1744, 1697, 1588, 1514, 1260, 1110 cm^{-1}; Anal. Calcd for $C_{21}H_{22}N_2O_4$ (366.42): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.72; H, 5.88; N, 7.48.

General reaction procedure for functionalized bis-tetrahyropyrimidines 7. A mixture of DMAD (1 mmol) and diamines (1 mmol) in MeOH (2 mL) was stirred at room teperatutre for 20 min. Aniline (2 mmol) in MeOH (1 mL) and formaldehyde (38%, 400 mg, 5 mmol) in methanol (2 mL) were added into it. Finally, the catalyst silica supported perchloric acid (50 mg, 2.5 mol %) was added into the reaction vessel. After completion of reaction as monitored by TLC, the same work up procedure was followed as above. The products **7a–e** were obtained by purification through column chromatography using ethyl acetate/hexane (1:9) as eluent.

Compound 7a. Light yellow solid (428 mg, 74%); mp 104–106°C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.98 (s, 4 H), 3.71 (s, 6 H), 3.88 (s, 6 H), 4.01 (s, 4 H), 4.44 (s, 4 H), 6.92–6.96 (m, 6 H), 7.25–7.29 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.3, 50.5, 51.6, 53.3, 67.9, 96.2, 118.1, 121.7, 129.6, 148.2, 148.5, 165.4, 166.2; IR (KBr): 2949, 1741, 1684, 1575, 1497, 1427, 1270, 1219, 1151, 1097 cm^{-1}; Anal. Calcd for $C_{30}H_{34}N_4O_8$ (578.63): C, 62.27; H, 5.92; N, 9.68. Found: C, 62.11; H, 5.83; N, 9.82.

Compound 7b. Yellow liquid (421 mg, 71%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (t, *J* = 7.2 Hz, 2 H), 2.90 (t, *J* = 7.2 Hz, 4 H), 3.69 (s, 6 H), 3.84 (s, 6 H), 4.04 (s, 4 H), 4.36 (s, 4 H), 6.93–6.96 (m, 6 H), 7.28 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 46.6, 48.6, 51.5, 53.1, 66.5, 95.3, 118.5, 121.8, 129.6, 148.7, 165.5, 166.3; IR (KBr): 2950, 1739, 1689, 1596, 1583, 1435, 1257, 1149 cm^{-1}; Anal. Calcd for $C_{31}H_{36}N_4O_8$ (592.65): C, 62.83; H, 6.13; N, 9.45. Found: C, 62.70; H, 6.02; N, 9.22.

Compound 7c. Yellow liquid (461 mg, 76%); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (br s, 4 H), 2.88 (br s, 4 H), 3.70 (s, 6 H), 3.85 (s, 6 H), 4.05 (s, 4 H), 4.43 (s, 4 H), 6.93 (t, *J* = 7.6 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 4 H), 7.62 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 46.3, 50.5, 51.3, 52.9, 66.1, 94.0, 118.2, 121.4, 129.4, 148.6, 148.9, 165.3, 166.3; IR (KBr): 2949, 1739, 1688, 1580, 1434, 1258, 1145 cm^{-1}; Anal. Calcd for $C_{32}H_{38}N_4O_8$ (606.68): C, 63.35; H, 6.31; N, 9.24. Found: C, 63.21; H, 6.11; N, 9.00.

Compound 7d. Yellow liquid (422 mg, 68%); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94–0.99 (m, 2 H), 1.25–1.32 (m, 4 H), 2.92 (t, *J* = 7.6 Hz, 4 H), 3.70 (s, 6 H), 3.85 (s, 6 H), 4.08 (s, 4 H), 4.09 (s, 4 H), 6.94 (t, *J* = 7.2 Hz, 2 H), 6.98 (d, *J* = 7.6 Hz, 4 H), 7.28 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 28.8, 46.5, 51.0, 51.4, 53.0, 66.4, 93.9, 118.4, 121.6, 129.5, 148.8, 149.0, 165.4, 166.4; IR (KBr): 2950, 1739, 1687, 1579, 1434, 1257, 1146, 1090 cm^{-1}; Anal. Calcd for $C_{33}H_{40}N_4O_8$ (620.70): C, 63.86; H, 6.49; N, 9.03. Found: C, 63.73; H, 6.43; N, 9.21.

Compound 7e. White solid (495 mg, 78%); mp 150–152°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (br s, 4 H), 1.33 (br s, 4 H), 2.96 (t, *J* = 7.2 Hz, 4 H), 3.70 (s, 6 H), 3.86 (s, 6 H), 4.09 (s, 4 H), 4.50 (s, 4 H), 6.93 (t, *J* = 7.2 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 4 H), 7.28 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 29.0, 46.5, 51.2, 51.4, 53.0, 66.4, 93.8, 118.4, 121.5, 129.5, 148.8, 149.1, 165.4, 166.4; Anal. Calcd for $C_{34}H_{42}N_4O_8$ (634.73): C, 64.34; H, 6.67; N, 8.83. Found: C, 64.30; H, 6.52; N, 8.69.

Crystallographic description of 7a. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Complete crystallographic data of **7a** has been deposited with the Cambridge Crystallographic Data Centre, CCDC no. is 756205. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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REFERENCES AND NOTES

[1] (a) Schreiber, S. L.; Science 2000, 287, 1964; (b) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. J Am Chem Soc 2009, 131, 1753; (c) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. J Am Chem Soc 2005, 127, 2836; (d) Trost, B. M. Angew Chem Int Ed 1995, 34, 259; (e) Trost, B. M. Acc Chem Res 2002, 35, 695.

[2] (a) Tietze, L. F.; Brazel, C. C.; Holsken, S.; Magull, J.; Ringe, A. Angew Chem Int Ed 2008, 47, 5246; (b) Yang, J. W.; Fonseca, H. M. T.; List, B. J. Am Chem Soc 2005, 127, 15036; (c) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raab, G. Nature 2006, 441, 861.

[3] (a) Zhu, J.; Bienaymé, H.; Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2006; (b) Tietze, L. F.; Brasche, G.; Gericke, K. M.; Domino Reactions in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2006; (c) Dömling, A. Chem Rev 2006, 106, 17.

[4] (a) Tietze, L. F. Chem Rev 1996, 96, 115; (b) Enders, D.; Huettl, M. R. M.; Grondal, C.; Raabe, G. Nature 2006, 441, 861.

[5] (a) Khan, A. T.; Parvin, T.; Choudhury, L. H. J Org Chem 2008, 73, 8398; (b) Khan, A. T.; Parvin, T.; Choudhury, L. H. Eur J Org Chem 2008, 5, 834; (c) Khan, A. T.; Khan, M. M.; Bannuru, K. K. R. Tetrahedron 2010, 66, 7762; (d) Khan, A. T.; Lal, M.; Khan, M. M. Tetrahedron Lett 2010, 51, 4419.

[6] (a) Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. Angew Chem Int Ed 2005, 44, 3879; (b) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. J Org Chem 1991, 56, 4574.

[7] (a) Messer, W. S.; Abuh, Y. F.; Liu, Y.; Periyasamy, S.; Ngur, D. O.; Edgar, M. A. N.; Eissadi, S.; Sbeih, A. A.; Dunbar, P. G.; Roknich, S.; Rho, T.; Fang, Z.; Ojo, B.; Zhang, H.; Huzl, J. J.; Nagy, P. I. J Med Chem 1997, 40, 1230. (b) Dunbar, P. G.; Durant, G. J.; Rho, T.; Ojo, B.; Huzl, J. J.; Smith, D. A.; El-Assadi, A. A.; Sbeih, S.; Ngur, D. O.; Periyassamy, S.; Hoss, W.; Messer, W. S. Jr. J Med Chem 1994, 37, 2774. (c) Dunbar, P. G.; Durant, G. J.; Fang, Z.; Abuh, Y. F.; El-Assadi, A. A.; Ngur, D. O.; Periyasamy, S.; Hoss, W. P.; Messer, W. S. J Med Chem 1993, 36, 842.

[8] (a) Nair, V.; Chi, G.; Ptak, R.; Neamati, N. J Med Chem 2006, 49, 445; (b) Zhou, S.; Kern, E. R.; Gullen, E.; Cheng, Y. C.; Drach, J. C.; Matsumi, S.; Mitsuya, H.; Zemlicka, J. J Med Chem 2004, 47, 6964.

[9] Chantrapromma, K.; James, S.; Manis, M.; Ganem, B. Tetrahedron Lett 1980, 21, 2475.

[10] Malin, G.; Iakobashvili, R.; Lapidot, A. J Biol Chem 1999, 274, 6920.

[11] (a) Endo, T.; Tsuda, M.; Fromont, J.; Kobayashi, J. J Nat Prod 2007, 70, 423; (b) Costa, E. V.; Pinheiro, M. L. B.; Xavier, C. M.; Silva, J. R. A.; Amaral, A. C. F.; Souza, A. D. L.; Barison, A.; Campos, F. R.; Ferreira, A. G.; Machado, G. M. C.; Leon, L. L. P. J Nat Prod 2006, 69, 292; (c) Lin, Y. L.; Huang, R. L.; Chang, C. M.; Kuo, Y. H. J Nat Prod 1997, 60, 982.

[12] (a) Zamri, A.; Sirockin, F.; Abdallah, M. A. Tetrahedron 1999, 55, 5157; (b) Shutalev, A. D.; Fesenko, A. A.; Cheshkov, D. A.; Goliguzov, D. V. Tetrahedron Lett 2008, 49, 4099.

[13] (a) Möhrle, H.; Reinhardt, H. W. Arch Pharm 1981, 314, 767; (b) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. J Org Chem 1985, 50, 4227; (c) Chanda, K.; Dutta, M. C.; Karim, E.; Vishwakarma, J. N. J Heterocycl Chem 2004, 41, 627; (d) Zhao, F.; Liu, J. J Fluorine Chem 2004, 125, 1491.

[14] (a) Qiuhua, Z.; Huanfeng, J.; Jinghao, L.; Min, Z.; Xiujun, W.; Chaorong Q. Tetrahedron 2009, 65, 4604; (b) Zhang, M.; Jiang, H.; Liu, H.; Zhu, Q. Org Lett 2007, 9, 4111; (c) Cao, H.; Wang, X.; Jiang, H.; Zhu, Q.; Zhang, M.; Liu, H. Chem Eur J 2008, 14, 11623.

[15] (a) Chakraborti, A. K.; Gulhane, R. Chem Commun 2003, 1896; (b) Misra, A.; Tiwari, P.; Agnihotri, G. Synthesis 2005, 260; (c) Kamble, V. T.; Jamode, V. S.; Joshi, N. S.; Biradar, R. A. V.; Deshmukh, Y. Tetrahedron Lett 2006, 47, 5573; (d) Du, Y.; Wei, G.; Cheng, S.; Hue, Y.; Linhardt, R. J. Tetrahedron Lett 2006, 47, 307; (e) Agarwal, A.; Rani, S.; Vankar, Y. D. J Org Chem 2004, 69, 6137; (f) Maheswara, M.; Siddaiah, V.; Rao, Y. K.; Tzeng, Y. -M.; Sridhar, C. J Mol Catal A Chem 2006, 260, 179; (g) Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L. J Mol Catal A Chem 2007, 266, 104; (h) Narasimhulu, M.; Reddy, T. S.; Mahesh, K. C.; Prabhkar, P.; Rao, C. B.; Venkateswarlu, Y. J Mol Catal A Chem 2007, 266, 114; (i) Kantevri, S.; Bantu, R.; Nagarapu, L. J Mol Catal A Chem 2007, 269, 53.

[16] (a) Khan, A. T.; Choudhury, L. H.; Ghosh, S. J Mol Catal A Chem 2006, 255, 230; (b) Khan, A. T.; Parvin, T.; Choudhury, L. H. Synthesis 2006, 15, 2497; (c) Khan, A. T.; Ghosh, S.; Choudhury, L. H. Eur J Org Chem 2006, 9, 2226.

[17] (a) Kumar, A.; Sharma, S.; Maurya, R. A. Tetrahedron Lett 2009, 50, 5937; (b) Reza, S. H.; Asghar, H.; Majid, G. Synth Commun 2008, 38, 3766.