A Novel and Efficient Lewis Acid Catalysed Preparation of Pyrimidines: Microwave-Promoted Reaction of Urea and β-Formyl Enamides

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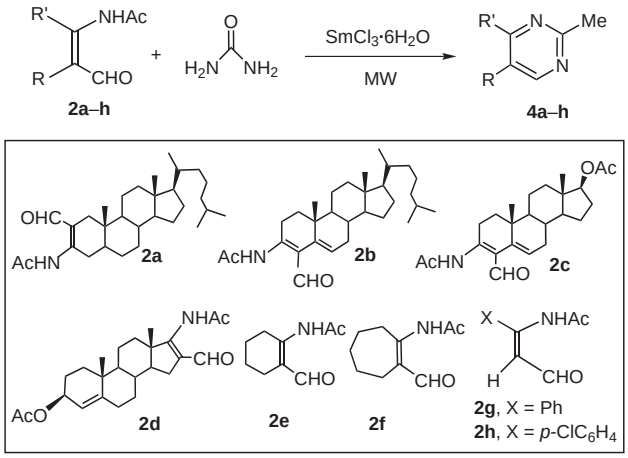
Abstract: A novel and efficient synthesis of pyrimidine from β-formyl enamide is described. The key step involves samarium chloride catalysed cyclisation of β-formyl enamides using urea as source of ammonia under microwave irradiation.

Key words: β-formyl enamide, urea, microwave, pyrimidine

Pyrimidines are a widespread heterocyclic motif found in numerous natural products and synthetic pharmacophores with antibacterial, antimicrobial, anticancer and antimycotic activities.[1] Pyrimidine derivatives are important since compounds such as 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and dihydroalkoxybenzyloxopyrimidines (DABO) showed important anti-HIV-1 activity[2,3] and structurally related pyrimidines exhibited antirubella virus activity.[4] The highly electron-deficient nature of the pyrimidine ring renders nucleophilic aromatic substitution (S_NAr) a general approach for synthesis of a large number of pyrimidine derivatives from corresponding halopyrimidines.[5] However, adequate synthetic methods to pyrimidines are limited and efforts are still being made to accomplish more general and versatile synthetic methods.[6]

Enamides constitute the building blocks of many biologically active compounds[7] and attract considerable attention as prochiral substrates in asymmetric synthesis of β-amino acids.[8] In our earlier efforts we accomplished the synthesis of β-formyl enamides from the Vilsmeier reaction of enamides or conjugated oximes.[9] Nevertheless, steroidal β-formyl enamides have shown interesting diversity as organic synthons.[10] Recently, we employed microwave energy[11] for the condensation of β-formyl enamides for one-pot synthesis of pyridines via the Henry reaction.[12]

As a part of our continuing research on heterosteroids,[13] herein we report an efficient one-pot synthesis of pyrimidines from β-formyl enamides employing urea and samarium chloride under microwave irradiation. Although Biginelli reaction represents an excellent example of the utility of urea as amine component for synthesis of



Scheme 1

3,4-dihydropyrimidine-2(1*H*)-one,[14] in contrast, we have demonstrated urea as an efficient source of ammonia in pyrimidine synthesis.

For example, irradiation of a finely ground mixture of 3-acetamido-2-formyl-5α-cholest-2-ene (**2a**) with 3.0 equivalents of urea and 1.5 molar equivalents of samarium chloride hexahydrate in an open vessel in a Prolabo Synthwave 402 microwave reactor for eight minutes at atmospheric pressure afforded 2′-methyl-5α-cholest[2,3-*e*]pyrimidine (**4a**) in 82% yield (Scheme 1).[15] The product was identified from spectroscopic and analytical data.[16]

The ^{1}H NMR of **4a** showed a singlet at δ = 8.28 for the aromatic proton of pyrimidine. The ^{13}C NMR spectra exhibited four characteristic signals for aromatic carbons at δ = 165.41, 165.35, 157.70 and 126.31. Similarly steroidal, acyclic and aliphatic formyl enamides **2b**–**h** reacted with urea in the presence of samarium chloride to afford annelated pyrimidines **4b**–**h** in high yields (Table 1, entries 2–8). However, when the same reaction was carried out in refluxing xylene for 3–4 hours, it failed to afford products **4a**–**h**.

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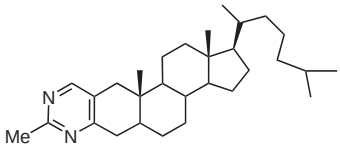
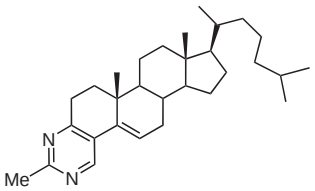
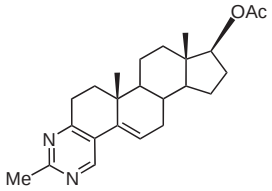
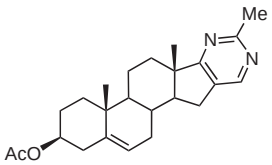
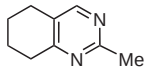
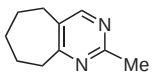
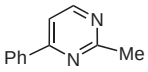
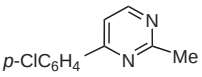
Table 1 Conversion of β-Formyl Enamides **2a**–**h** to Pyrimidines **4a**–**h** Using Urea and $SmCl_3·6H_2O$ under Microwave Irradiation[a]

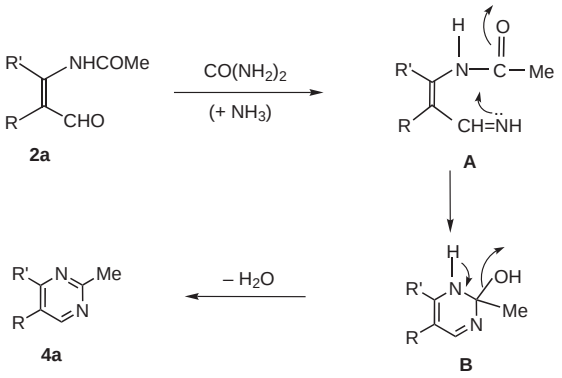
Entry	β-Formyl enamides	Reaction time (min)	Product	Yield (%)[b]
1	**2a**	8	 **4a**	82
2	**2b**	10	 **4b**	84
3	**2c**	10	 **4c**	80
4	**2d**	9	 **4d**	86
5	**2e**	8	 **4e**	78
6	**2f**	8	 **4f**	79
7	**2g**	10	 **4g**	80
8	**2h**	10	 **4h**	84

[a] The reactions were carried out in the solid phase.
[b] Isolated yields.

In the absence of samarium chloride, the microwave-mediated reaction of **2a** with urea was found to be sluggish, and there was a considerable decrease in the yield of product **4a**. It was presumed that samarium chloride, being a Lewis acid with coordinating properties,[17] played a key role as a catalyst in the pyrimidine formation.

A mechanism is proposed via amination of **2a** followed by cyclisation reaction. Under microwave heating, urea released ammonia[18] which combined with **2a** to afford imine intermediate **A**. Samarium chloride presumably catalysed the reaction by activating the carbonyl group of amide intermediate **A**, thus facilitating imine cyclisation to **B** with subsequent loss of water to afford product **4a** (Scheme 2).

To study the influence of Lewis acid on pyrimidine formation, we carried out solid-phase cyclisation reactions of **2a**, **2d** and **2e** with urea using $BF_3·OEt_2$, anhydrous $AlCl_3$ and $TiCl_4$. As shown in Table 2, the products **4a**, **4d** and **4e** were obtained in good yields in each case.



Scheme 2

Table 2 Effect of Lewis Acids on Cyclisation Reaction of β-Formyl Enamides with Pyrimidines under Microwave Irradiation

Entry	β-Formyl enamides	Lewis acid	Product	Yield (%)
1	**2a**	$BF_3{\cdot}OEt_2$	**4a**	72
2	**2a**	$AlCl_3$	**4a**	70
3	**2a**	$TiCl_4$	**4a**	68
4	**2d**	$BF_3{\cdot}OEt_2$	**4d**	70
5	**2d**	$AlCl_3$	**4d**	66
6	**2d**	$TiCl_4$	**4d**	65
7	**2e**	$BF_3{\cdot}OEt_2$	**4e**	75
8	**2e**	$AlCl_3$	**4e**	70
9	**2e**	$TiCl_4$	**4e**	71

In conclusion, we have developed a novel strategy for the preparation of annelated pyrimidines from the one-pot reaction of β-formyl enamide with urea under microwave irradiation. The cyclisation reaction was found to be catalysed by Lewis acids such as trivalent samarium chloride. In contrast to the role of urea as amine component in Biginelli reaction,[14] we successfully demonstrated the utility of urea as an environmentally benign and safe source of ammonia in pyrimidine synthesis. The method reported herein represents a new application of β-formyl enamides and is expected to be a general route for facile and combinatorial synthesis of a wide range of annelated pyrimidines. Further synthetic application of the newly developed β-formyl enamide system is in progress.

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(15) **Representative Procedure for the Synthesis of 2′-Methyl-5α-cholest[2,3-*e*]pyrimidine (4a)**:
3-Acetamido-2-formyl-5α-cholest-2-ene (**2a**; 0.46 g, 1 mmol), urea (0.18 g, 3.0 mmol) and samarium chloride hexahydrate (0.55 g, 1.5 mmol) were mixed intimately in a mortar and irradiated in an open reaction vessel of a Synthwave 402 Prolabo focused microwave reactor (manufactured by M/s Prolabo, 54 rue Roger Salengro, Cedex, France) after setting the reaction temperature at 140 °C and the power at 80% (maximum output 300 Watts). On completion of reaction (vide TLC), the reaction mixture was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic portion was washed with H_2O, dried over anhyd Na_2SO_4 and the solvent was removed to obtain a crude product. Column chromatography separation using EtOAc–hexane (1:9) as eluent over silica gel afforded **4a** in 82% yield. This procedure was followed for the synthesis of all products listed in Table 1.

(16) Spectral and analytical data of selected compounds:
Compound 4a: mp 90–92 °C; R_f = 0.3 (EtOAc–hexane, 20:80). IR (KBr): 2925, 1641, 1582, 1559, 1442 cm^{-1}. ^1H NMR (300 MHz. $CDCl_3$): δ = 8.28 (br s, 1 H), 2.65 (s, 3 H), 0. 96 (s, 3 H), 0.74 (s, 3 H), 0.91–2.78 (m, 38 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 165.4, 157.7, 126.3, 56.8, 54.1, 42.9 (3 × C), 39.9 (2 × C), 36.6, 36.4, 36.1 (2 × C), 35.4, 31.9, 30.0, 28.9, 28.5, 28.3, 25.8, 24.6, 24.2, 23.1, 22.9, 21.7, 19.1, 12.4, 11.9. MS (ESI): *m*/*z* = 437 [M^+ + 1]. Anal. Calcd for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08; N, 6.41. Found: C, 82.28; H, 10.95; N, 6.59.
Compound 4b: gum; R_f = 0.3 (EtOAc–hexane, 30:70). IR (KBr): 2925, 1631, 1578, 1552, 1440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br s, 1 H), 6.19 (br s, 1 H), 2.64 (s, 3 H), 0.94 (s, 3 H), 0.88 (s, 3 H), 1.00–2.82 (m, 35 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 161.9, 160.0, 154.4, 126.3, 122.5, 56.6, 56.3, 54.2, 42.8, 40.1, 39.9 (2 × C), 39.5, 38.5, 36.5, 36.4, 36.2, 32.5, 31.6, 28.6, 28.4, 26.1, 24.7, 24.2, 23.2, 23.0, 19.1, 18.0, 12.3. MS (ESI): *m*/*z* = 435 [M^+ + 1].
Compound 4d: mp 165–67 °C; R_f = 0.3 (EtOAc–$CHCl_3$, 10:90). IR (KBr): 2943, 1735, 1668, 1594, 1555, 1420, 1245, 1033, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 5.35 (br s, 1 H), 4.52 (m, 1 H), 2.62 (s, 3 H), 1.97 (s, 3 H), 1.03 (s, 3 H), 0.92 (s, 3 H), 1.06–2.66 (m, 17 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9, 170.7, 166.5, 152.0, 140.7, 130.8, 122.1, 74.1, 56.2, 51.0, 46.3, 38.5, 37.3, 33.2, 31.7, 31.2, 29.1, 28.3, 28.1, 26.2, 21.6, 20.8, 19.7, 17.2. MS (ESI): *m*/*z* = 381 [M^+ + 1]. Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.90; H, 8.64; N, 7.17.
Compound 4e: oil; R_f = 0.3 (EtOAc–$CHCl_3$, 20:80). IR (KBr): 2925, 1641, 1583, 1553, 1438 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.29 (s 1 H), 2.83 (t, *J* = 5.96 Hz, 2 H), 2.70 (t, *J* = 6.05 Hz, 2 H), 2.65 (s, 3 H), 1.80–1.93 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.2, 157.2, 127.0, 32.1, 25.8, 25.5, 22.6, 22.5. MS (ESI): *m*/*z* = 149 [M^+ + 1].
Compound 4h: mp 91–93 °C; R_f = 0.5 (EtOAc–$CHCl_3$, 10:90). IR (KBr): 2924, 1655, 1578, 1545, 1435, 825, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 5.34 Hz, 1 H), 8.03 (d, *J* = 8.55 Hz, 2 H), 7.46–7.49 (m, 3 H), 2.80 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 163.2, 158.1, 137.5, 135.7, 129.6 (2 × C), 128.9 (2 × C), 114.1, 26.7. MS (ESI): *m*/*z* = 205 [M^+ + 1]. Anal. Calcd for $C_{11}H_9N_2Cl$: C, 64.55; H, 4.43; N, 13.68. Found: C, 64.41; H, 4.33; N, 13.40.

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