A facile route to the synthesis of novel 2-amino-1,4,5,6-tetrahydropyrimidines from Baylis-Hillman products of acrylonitrile[1]

Richa Pathak, Amrendra K. Roy and Sanjay Batra*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow-226001 India

Fax: +91-522-2623405, 2623938.

E-mail: batra_san@yahoo.co.uk

Abstract: A facile route for the synthesis of novel 5-substituted-2-amino-1,4,5,6-tetrahydro pyrimidines from the Baylis-Hillman adducts obtained from reaction of aldehydes and acrylonitrile is described.

Key words: Baylis-Hillman, 2-amino-1,4,5,6-tetrahydropyrimidines, 5,6,7,8-tetrahydro-2*H*-imidazo[1,2-a] pyrimidin-3-one.

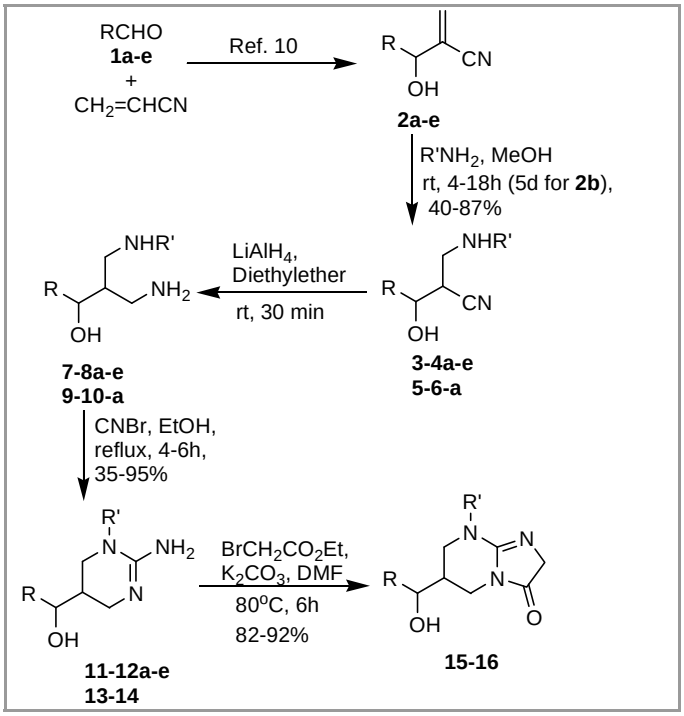
The Baylis-Hillman reaction has been one of the most intensively studied C-C bond forming reactions of present times. The major reason for the success of this reaction has been the ease with which it can be performed and the synthetic utility of multifunctional products obtained. These products are suitable substrates for further elaboration into useful molecular frameworks including heterocycles and natural products.[2,3]

The Nitrogen-containing heterocyclic frameworks not only form the basic skeleton of innumerable natural products but are also key structural components of several drugs. Although a variety of nitrogen heterocycles have already been generated through Baylis Hillman chemistry,[4] we were specifically interested in the generation of nitrogen containing heterocyclic structures having the cyclic guanidine pharmacophore since such heterocycles are of immense biological significance.[5-8] It was envisaged that the Baylis-Hillman product of acrylonitrile and the aldehyde may offer entry into appropriately substituted 2-amino-1,4,5,6-tetrahydropyrimidine derivatives, a facile synthesis of which has only recently been reported.[9] In principle, the Michael addition of a primary amine to the double bond of the Baylis-Hillman adduct followed by reduction of the nitrile group would result in a diamino-derivative which could lead to the desired compounds. Thus, we examined the possibility and report herein our preliminary attempts on the development of a facile route for the synthesis of 2-amino-1,4,5,6-tetrahydro-pyrimidines.

The synthesis of the title compounds is outlined in scheme1. The Baylis-Hillman reaction of several aldehydes with acrylonitrile was carried out according to the literature procedure[10] to obtain the corresponding Baylis-Hillman adducts **(2a-e)** in excellent yields. The Michael reaction of different primary amines with adducts **(2a-e)** led to the amino derivatives **3-4a-e, 5-6a**. Interestingly, though most reactions were complete within 4-18h, reactions of compound **2b** took 5 days. Reduction of amino derivatives **(3-4a-e, 5-6a)** to the corresponding diamines **(7-8a-e, 9-10a)** was accomplished in high yields through the action of $LiAlH_4$. As the purification of diamines led to significant loss of yields, these compounds **(7-8a-e, 9-10a)** were used as crude for further reactions. Treatment of diamines **7-8a-e, 9-10a** with cyanogen bromide then afforded the 2-amino-1,4,5,6-tetrahydro-pyrimidines **11-12a-e, 13-14** in moderate to good yields.[11] As expected these compounds were obtained as diastereoisomeric mixtures. To assess the general applicability of this synthetic strategy we have utilized different Baylis-Hillman adducts and amines (Table 1).

The 2-amino-1,4,5,6-terahydro-pyrimidines described herein are amenable for further elaboration. For example, they can be readily converted to 5,6,7,8-tetrahydro-2H-imidazo[1,2-a]pyrimidin-3-ones employing bromoethyl acetate. Therefore, the reaction of compounds **11e** and **12c** with bromoethyl acetate in the presence of potassium carbonate afforded the products **15** and **16**, respectively in excellent yields.[12]

Thus, we have presented a very simple synthetic strategy to obtain 5-substituted-2-amino-1,4,5,6-tetrahydro-pyrimidines utilizing Baylis-Hillman adducts. Further work is underway to understand the scope and limitations of this strategy to generate variety of annulated systems using these pyrimidines.



Scheme 1. For key to R refer to Table 1.

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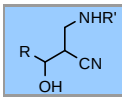
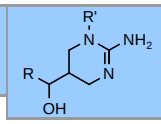
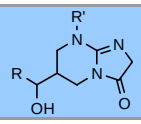
Table 1 Table 1. Yields and physical characteristics of new compounds.[a]

Entry	R	R'	Compd. No., Yield, appearance, mp (°C), ν_{max} (cm^{-1}) CN, OH	Compd. No., Yield, appearance, mp (°C), Mass (ES+ or FAB+), ν_{max} (cm^{-1}) OH and NH_2	Compd. No., Yield, appearance, mp (°C) Mass (ES+ or FAB+), ν_{max} (cm^{-1}) C=O, OH
					
1	C_6H_5	$C_6H_5CH_2$	**3a**, 75, Colorless sticky solid	**11a**, 40, Yellow sticky solid, 296, 3420	
2	4-Cl-C_6H_4	$C_6H_5CH_2$	**3b**, 40, brown oil	**11b**, 95, Yellow oil, 330, 3393	
3	3-Phenyl-isoxazol-5-yl	$C_6H_5CH_2$	**3c**, 58, Brown oil	**11c**, 84, Brown solid, 85-87, 363.60, 3377	
4	3-(4-Methyl-phenyl)-isoxazol-5-yl	$C_6H_5CH_2$	**3d**, 68, Brown solid	**11d**, 49, Brown solid, 162-164, 378, 3405	
5	3-(2-Chloro-phenyl)-isoxazol-5-yl	$C_6H_5CH_2$	**3e**, 71, Yellow oil	**11e**, 40, Brown solid, 90-92, 397.67, 3352	**15**, 92, Brown oil, 437.47, 1662, 3408
6	C_6H_5	4-F- $C_6H_4CH_2$	**4a**, 72, Yellow oil	**12a**, 44, Colorless solid, 210-212, 314, 3343	
7	4-Cl-C_6H_4	4-F- $C_6H_4CH_2$	**4b**, 41, Brown oil	**12b**, 91, Yellow oil, 348.73, 3335	
8	3-Phenyl-isoxazol-5-yl	4-F- $C_6H_4CH_2$	**4c**, 62, Colorless solid, 135-137	**12c**, 57, Brown oil, 381, 3370	**16**, 82, Brown oil, 421
9	3-(4-Methyl-phenyl)-isoxazol-5-yl	4-F- $C_6H_4CH_2$	**4d**, 76, Off white solid, 79-81	**12d**, 35, Colorless solid, 229-230 (dec), 396, 3401	
10	3-(2-Chloro-phenyl)-isoxazol-5-yl	4-F- $C_6H_4CH_2$	**4e**, 86, Light brown oil	**12e**, 44, Brown solid, 98-100, 415.33, 3353	
11	C_6H_5	Cyclohexyl	**5a**, 87, Colorless solid, 164-166	**13**, 89, Yellow oil, 289, 3424	
12	C_6H_5	$CH_3(CH_2)_3$	**6a**, 84, Off white solid, 122-124	**14**, 88, Colorless solid, 178-179, 262.3, 3379	

[a] All compounds gave satisfactory microanalyses

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(11) *General Procedure for the synthesis of 1,4,5,6-tetrahydro-pyrimidines* (**11-12a-e, 13-14**). A solution of appropriate diamines from 7-**8a-e, 9-10a** (2.3 mmol) and cyanogen bromide (2.3 mmol, 0.243g) in absolute ethanol (5mL) was allowed to stir at 80°C for 4-6h. Thereafter the excess solvent was evaporated and the reaction mixture was washed with 10% aq. $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and evaporated to furnish a residue. The residue upon triturating with hexane or through column chromatography (Chloroform: MeOH, 9.5: 0.5, v/v) yielded the pyrimidines. Representative data (as diastereoisomeric mixture) of 2-amino-1, 4, 5, 6-tetrahydro pyrimidines: **11e**- ^{1}H NMR (300 MHz, $CDCl_3$+TFA_d) δ 2.66-2.71 (m, 2H, 2 X CH), 3.28-3.63 (m, 8H, 2 X CH_2-NH and 2 X CH_2-N), 4.49, 4.53 (2s, 4H, 2 X CH_2-Ph), 4.95, 5.01 (2d, 2H, 2 X CH-OH), 6.67, 6.73 (2s, 2H, 2 X =CH), 7.19-7.64 (m, 18H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$+TFA_d) δ 35.9, 36.1, 39.4, 40.4, 47.5, 48.0, 53.9, 54.2, 65.3, 66.1, 105.3, 109.0, 112.8, 116.5, 120.3, 124.7, 126.2, 126.9, 127.1, 127.7, 129.3, 129.4, 129.8, 130.1, 130.3, 130.9, 131.0, 132.4, 132.7, 132.8, 133.2, 134.7, 148.7, 154.0, 171.0, 171.1; $C_{21}H_{21}ClN_4O_2$ requires C, 63.55; H, 5.33; N, 14.12. Found: C, 63.19; H, 5.58; N, 13.88. **12d**- ^{1}H NMR (300 MHz, $CDCl_3$+ TFA_d) δ 2.42 (s, 6H, 2 X CH_3), 2.69 (brs, 2H, 2 X CH), 3.31-3.35 (m, 2H, 2

X 1H of CH_2-NH), 3.48-3.59 (m, 6H, 2 X CH_2-N and 2 X 1H of CH_2-NH), 4.49, 4.52 (2s, 4H, 2 X CH_2-Ph), 4.95, 5.01 (2d, 2H, 2 X CH-OH), 6.58, 6.67 (2s, 2H, 2 X =CH), 7.05-7.33 (m, 12H, ArH), 7.55 (d, 4H, *J*= 8.0 Hz, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$+TFA_d) δ 20.8, 21.6, 36.0, 36.4, 39.5, 40.3, 47.2, 47.8, 53.1, 53.2, 65.4, 66.2, 101.4, 109.2, 113.0, 116.7, 116.8, 116.9, 120.6, 124.3, 127.0, 128.8, 128.9, 129.0, 129.1, 129.6, 130.2, 130.7, 141.9, 154.1, 163, 164.8, 171.8, 171.9, 178.4; $C_{22}H_{23}FN_4O_2.H_2O$ requires C, 64.06; H, 6.11; N, 13.58. Found: C, 63.91; H, 6.18; N, 13.72.

(12) *General Procedure for the synthesis of 5, 6, 7, 8-tetrahydro-2H-imidazo[1,2-a]pyrimidin-3-ones* (**15, 16**). To the solution of compound **11e** or **12c** (0.63 mmol) in dry DMF was added K_2CO_3 (0.63 mmol, 0.104g) and bromoethyl acetate (0.63 mmol, 0.28 mL) and the mixture was heated at 80^{o}C under stirring for 6h. Then the reaction mixture was extracted with ethyl acetate and water. The usual work up of the organic layer afforded a residue that upon column chromatography over silica gel using hexane: ethyl acetate (70:30, v: v) yielded the pure compound as oils. Representative data (as diastereoisomeric mixture) of 5,6,7,8-tetrahydro-2H-imidazo[1,2-a]pyrimidin-3-ones: **15** ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62-3.44 (m, 10H, 2 X CH_2-NH, 2 X CH_2-N and 2 X CH), 3.86-3.93 (m, 8H, 2 X CH_2CO and 2 X CH_2-Ph), 4.52, 4.57 (2d, 2H, *J*= 3.8 Hz, 2 X CH-OH), 6.47, 6.67 (2s, 2H, 2 X =CH), 7.22-7.64 (m, 18H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$+TFA_d) δ 36.7, 36.9, 42.3, 43.5, 45.0, 45.7, 54.1, 54.3, 56.2, 65.1, 65.7, 103.8, 127.4, 128.4, 128.6, 129.1, 130.7, 131.1, 131.3, 133.1, 135.8, 161.2, 167.8, 172.5, 172.8, 185.1, 185.4. $C_{23}H_{21}ClN_4O_3$ requires C, 63.23; H, 4.84; N, 12.82. Found: C, 63.10; H, 5.01; N, 13.07.