J. Indian Chem. Soc.,
Vol. 92, June 2015, pp. 839-842

A novel and one pot synthesis of ethyl 7,12-dihydro-1,3,6,7,12-pentaazapleiadene-5-carboxylates

Vishnu Basetti[a,b], Venkatanarayana Poturaju[a], Subramanya Hosahalli[a] and Vijay Potluri*[a]

[a]Department of Discovery Chemistry, Aurigene Discovery Technologies Ltd., Hyderabad-500 049, Telangana, India

E-mail : vijay_p@aurigene.com, potluri.vijay@gmail.com

[b]JNT University, Kukatpally, Hyderabad-500 072, Telangana, India

Abstract : A new tandem three-step synthesis of ethyl 7,12-dihydro-1,3,6,7,12-pentaazapleiadene-5-carboxylate derivatives (9a-j) has been accomplished stepwise. Reaction of 4-chloro-6-methylpyrimidine-5-carbonitrile with various 4-substituted 2-nitrobenzeneamines yielded the corresponding 4-(2-nitrophenylamino)-6-methylpyrimidine-5-carbonitriles (7a-j). These phenylamino methylpyrimidines reacted with diethyl oxalate to furnish (Z)-ethyl 3-(6-(2-nitrophenylamino)-5-cyanopyrimidin-4-yl)-2-hydroxyacrylates (8a-j). The resulting (Z)-ethyl 3-(6-(2-nitrophenylamino)-5-cyanopyrimidin-4-yl)-2-hydroxyacrylates on reduction with $SnCl_2.2H_2O$ in ethanol underwent cyclization to afford the desired products in good to very good yields.

Keywords : 4-Chloro-6-methylpyrimidine-5-carbonitrile, pentaazapleiadenes, stannous chloride, domino method.

Introduction

Fused pyrimidine compounds are of significant importance in chemical biology and medicinal chemistry, due to their therapeutic properties[1]. In particular, pyrido and pyrimidobenzodiazepiene derivatives have shown interesting pharmacological properties; for example, 7-azasampangine (**1**) was reported to show considerable antimicrobial activity[2] and *in vivo* studies on olanzapine (**2**) have established its antipsychotic activity[3]. Similarly pyrimidobenzodiazepinone (**3**) have shown immunosuppressive activity[4]. In view of these findings in literature we designed a novel ethyl pentaazapleiadene carboxylate (**9**) (Fig. 1) to imitate the molecular frames of 7-azasampanzine, olanzapine and compound (**3**) for the possibility that the title compounds might have potential as antimicrobials and/or antipsychotics and/or immunosuppressive agents.

We report here in an efficient synthesis of ethyl 7,12-dihydro-1,3,6,7,12-pentaazapleiadene-5-carboxylate derivatives involving domino reaction and ethyl 4-(2-aminophenoxy)-5,6-dihydro-5-oxopyrido[4,3-*d*]pyrimidine-7-carboxylates.

Results and discussion

Recently, we disclosed a novel methodology involving an acid mediated domino reaction for synthesis of tetracyclic 7-azasampangine (**1**)[5]. This protocol prompted us to develop a novel method to build the complex tetracyclic ethyl pentaazapleiadene carboxylate (**9**).

As presented in Scheme 1 the synthesis of the starting 4-chloro-6-methylpyrimidine-5-carbonitrile (**6**) was afforded in three-step reaction sequence starting from commercially available cyanoacetamide. At first, 4-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**5**) was readily

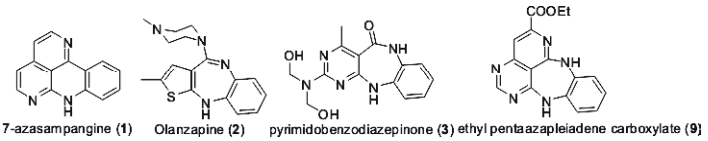
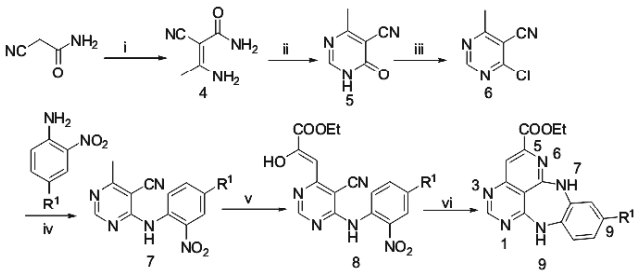


Fig. 1

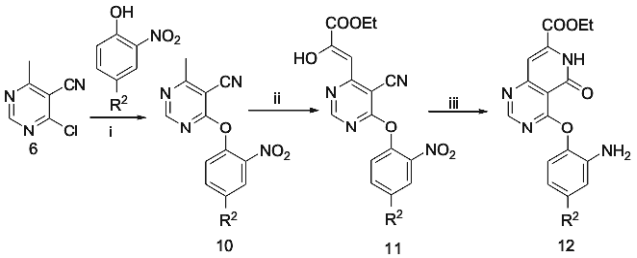
obtained according to the previously described procedure[6]. Further treatment of **5** with $POCl_3$ in the presence of triethylamine in toluene resulted in the formation of 4-chloro-6-methylpyrimidine-5-carbonitrile (**6**)[7] in very good yield 87%. The reaction of 4-chloro-6-methylpyrimidine-5-carbonitrile (**6**) with the appropriate 4-substituted 2-nitrobenzeneamines carried out at 120–130 °C for 1 h afforded the phenylamino methylpyrimidine intermediates (**7a-j**). Intermediates (**10k-l**) were obtained by reacting compound **6** with various 4-substituted 2-nitrophenols. The intermediate **7** and **10** upon treatment with diethyl oxalate in the presence of the lithium hexamethyldisilazide (LiHMDS) yielded (*Z*)-ethyl 3-(6-(2-nitrophenylamino)-5-cyanopyrimidin-4-yl)-2-hydroxyacrylates (**8a-j**) and (*Z*)-ethyl 3-(6-(2-nitrophenoxy)-5-cyanopyrimidin-4-yl)-2-hydroxyacrylates (**11k-l**) respectively in moderate yields as reported[8].



Reagents and conditions : (i) Acetamidine hydrochloride (1 equiv.), Na (1 equiv.), EtOH, at 0 °C to rt (24 h), reflux, 2 h; (ii) $HC(OEt)_3$ (10 mL/g), $(CH_3CO)_2O$ (10 mL/g), 140 °C, 3.5 h; (iii) Et_3N (0.2 equiv.), $POCl_3$ (1 equiv.), toluene, 100 °C, 12 h; (iv) neat 120–130 °C, 1 h; (v) diethyl oxalate (2 equiv.), LiHMDS (2 equiv.), dry THF, at –78 °C to rt, 16 h; (vi) $SnCl_2.2H_2O$ (5 equiv.), EtOH, reflux, 18 h.

Scheme 1

Intermediates **8a-j**, due to the key functionalities of nitro on benzene, a cyano and an enol, functional groups on sequential carbon atoms of the pyrimidine underwent domino reaction in the presence of $SnCl_2.2H_2O$ in ethanol afforded the novel pentaazapleiadene ring system (**9a-j**) (Scheme 1). Table 1 summarizes the yields for the transformation from **6** to **9a-j** for various derivatives. However, when 4-substituted 2-nitro phenols were used in place of the 2-nitro anilines in presence of $SnCl_2.2H_2O$ in ethanol, the corresponding phenoxypyridopyrimidine derivatives **12k-l** were obtained (Table 1 : entries **k** to **l**) (Scheme 2).

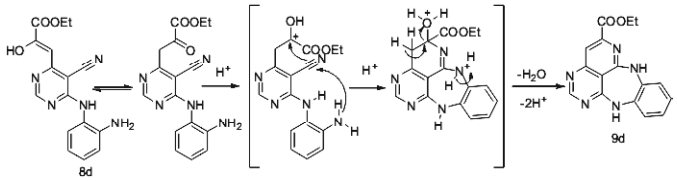


Reagents and conditions : (i) K_2CO_3 (2 equiv.), DMF, rt, 0.5 h; (ii) diethyl oxalate (2 equiv.), LiHMDS (2 equiv.), dry THF, at –78 °C to rt, 16 h; (iii) $SnCl_2.2H_2O$ (5 equiv.), EtOH, reflux, 18 h.

Scheme 2. Synthesis of **12**.

Table 1

Entry	Anilines (R^1)	**7** (Yield %)	**8** (Yield %)	**9** (Yield %)
a	OMe	72	60	88
b	Me	72	62	82
c	Et	74	65	85
d	H	74	58	72
e	$CH(CH_3)_2$	72	61	80
f	OEt	77	64	79
g	Ph	76	65	75
h	F	68	59	60
i	Cl	65	56	62
j	Br	64	50	56
Entry	Phenols (R^2)	**10** (Yield %)	**11** (Yield %)	**12** (Yield %)
k	H	79	63	70
l	Cl	78	57	68



Scheme 3. Proposed mechanism for the formation of ethyl 7,12-dihydro-1,3,6,7,12-pentaazapleiadene-5-carboxylate.

Experimental

General consideration : Melting points were determined on a Buchi melting point B-540 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were obtained on Varian 400 MHz spectrometer. Mass spectra were obtained on API 2000 Perkin-Elmer (PE-SCIEX) mass spectrometer. High resolution mass spectra were recorded Q-TOF LC/MS 6510 series classic G6510A (Agilent Technologies) mass spectrometer with an ESI source. IR spectra were recorded on an IRPrestage-21 FTIR spectrometer.

General procedure for the preparation of **7a-j** : 4-Chloro-6-methylpyrimidine-5-carbonitrile (**7**) (6.54 mmol) and 2-nitro aniline (6.23 mmol) were heated at 130 °C for a period of 30 min and cooled to room temperature. The reaction mixture was treated with 50 mL water, pH adjusted to ~9 with saturated Na_2CO_3 solution and stirred for 20 min. The solid obtained was filtered and dried under vacuum to furnish the desired products.

4-((4-Methoxy-2-nitrophenyl)amino)-6-methylpyrimidine-5-carbonitrile **(7a)** : Yield : 72%, m.p. 186–188 °C; IR (KBr) : 3259, 2918, 2833, 2218, 1604, 1556, 1519, 1334, 1236, 1024, 858 cm^{-1}; ^{1}H NMR (DMSO-d_6) : δ 10.02 (1H, s), 8.48 (1H, s), 7.61 (1H, d, *J* 8.8 Hz), 7.57 (1H, d, *J* 2.8 Hz), 7.35 (1H, dd, J_1 8.8 Hz, J_2 3.2 Hz), 3.87 (3H, s), 2.54 (3H, s); MS (ES) *m/z* : 286 (M^++1).

General procedure for the preparation of **10k-l** : To a solution of 2-nitro phenol (5.23 mmol) and potassium carbonate (10.46 mmol) in dry DMF (15 mL), 4-chloro-6-methylpyrimidine-5-carbonitrile (**7**) (5.23 mmol) was added, and the reaction mixture was stirred at room temperature for 45 min. The mixture was treated with 100 mL water and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried (anhydrous Na_2SO_4) and evaporated to dryness to furnish the desired products.

4-Methyl-6-(2-nitrophenoxy)pyrimidine-5-carbonitrile (**10k**) : Yield : 79%, m.p. 100–102 °C; IR (KBr) : 2915, 2218, 1608, 1558, 1516, 1330, 1246, 1022, 856 cm^{-1}; ^{1}H NMR (DMSO-d_6) : δ 8.88 (1H, s), 8.32 (1H, dd, J_1 8.4 Hz, J_2 2 Hz), 8.01–7.97 (1H, m), 7.75–7.70 (2H, m), 2.79 (3H, s); MS (ES) *m/z* : 255 (M^+–1).

General procedure for the preparation of **8a-j** *and* **11k-l** :

To a solution of 5-cyano-6-methylpyrimidines (**8a-j** and **11k-p**; 4.7 mmol) in dry THF (30 mL) was added dropwise lithium hexamethyldisilazide (1 *M* solution in THF, 9.3 mL, 9.4 mmol) at –78 °C under nitrogen. The reaction mixture was stirred for 30 min and then diethyl oxalate (9.3 mL, 9.4 mmol) was added in a single portion. The mixture was then allowed to warm to 0 °C and stirred for 30 min then slowly to allowed to reach room temperature and the stirring continued for 15 h. The reaction mixture was quenched by diluted hydrochloric acid at 0 °C. Then added water (150 mL), the precipitated solid was filtered and dried under vacuum to furnish the desired products.

(Z)-Ethyl 3-(5-cyano-6-((4-methoxy-2-nitrophenyl)-amino)pyrimidin-4-yl)-2-hydroxyacrylate (**8a**) : Yield : 60%, m.p. 237–239 °C; IR (KBr) : 3244, 2845, 2212, 1732, 1620, 1529, 1363, 1251, 1176, 1035, 914, 829, 775 cm^{-1}; ^{1}H NMR (DMSO-d_6) : δ 14.32 (1H, br s), 10.52 (1H, s), 8.38 (1H, s), 7.58 (1H, d, *J* 3.2 Hz), 7.53 (1H, d, *J* 8.8 Hz), 7.36 (1H, dd, J_1 8.8 Hz, J_2 3.2 Hz), 6.11 (1H, s), 4.24 (2H, q, *J* 6.8 Hz), 3.87 (3H, s), 1.27 (3H, t, *J* 6.8 Hz); MS (ES) *m/z* : 386 (M^++1).

General procedure for preparation of tetracyclic ethyl pentaazapleiadene carboxylates and ethyl 2-aminophenoxy cyanopyrimidine hydroxyacrylates **(9a-j** *and* **12k-l)** : To a solution of hydroxyacrylates (**8a-j** and **11k-p**; 0.84 mmol) in ethanol (20 mL) was added $SnCl_2.2H_2O$ (4.2 mmol) and the mixture was refluxed for 18 h. The mixture was cooled and poured into water and basified to pH ~9 (saturated aq. Na_2CO_3) and was extracted with ethyl acetate. The organic layer was washed with water, brine, dried (anhydrous Na_2SO_4), concentrated and purified by flash column chromatography (silica gel, 100–200 mesh) using 1–2% (v/v) methanol in dichloromethane as eluent.

Ethyl 9-methoxy-7,12-dihydro-1,3,6,7,12-pentaazapleiadene-5-carboxylate **(9a)** : Yield : 88%, m.p. 290–292 °C; IR (KBr) : 3344, 2933, 1735, 1598, 1535, 1342, 1226, 1126, 896 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) : δ 10.11 (1H, s), 9.42 (1H, s), 8.67 (1H, s), 7.58 (1H, s), 7.04 (1H, d, *J* 8.8 Hz), 6.87 (1H, d, *J* 2.8 Hz), 6.48 (1H, dd, J_1 8.8 Hz, J_2 2.8 Hz), 4.37 (2H, q, *J* 7.2 Hz), 3.68 (3H, s), 1.34 (3H, t, *J* 7.2 Hz); ^{13}C NMR (400 MHz, DMSO-d_6) : δ 164.1, 158.6, 158.2, 157.3, 156.4, 154.9, 147.1, 132.6, 122.2, 121.7, 115.0, 108.1, 105.9, 99.8,

61.3, 55.1, 14.1; MS (ES) *m/z* : 338 (M^++1); HRMS (ESI) *m/z* Calcd. for $C_{17}H_{16}N_5O_3^+$ $[M+H]^+$ 338.1253, Found : 338.1241.

Conclusion

We have synthesized a variety of tetracyclic ethyl pentaazapleiadene carboxylates utilizing our domino methodology. In this methodology stannous chloride plays the dual role of reducing the nitro group and provides the required acidic conditions to initiate the domino reaction (Scheme 3).

Acknowledgement

The authors thank Aurigene Discovery Technologies Ltd. for financial support and also thank Jawaharlal Nehru Technological University for encouragement. The support from analytical department is gratefully acknowledged.

References

1. S. Wang, A. Folkes, I. Chuckowree, X. Cockcroft, S. Sohal, W. Miller, J. Milton, S. P. Wren, N. Vicker, P. Depledge, J. Scott, L. Smith, H. Jones, P. Mistry, R. Faint, D. Thompson and S. Cocks, *J. Med. Chem.*, 2004, **47**, 1329.
2. K. Mink and F. Bracher, *Arch. Pharm. Chem. Life Sci.*, 2007, **340**, 429.
3. D. O. Calligaro, J. Fairhurst, T. M. Hotten, N. A. Moore and D. E. Tupper, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 25.
4. J. Cobo, M. Nogueras, J. N. Low and R. Rodriguez, *Tetrahedron Lett.*, 2008, **49**, 7271.
5. V. Basetti, R. Pallepati, S. Hosahalli and V. Potluri, *Tetrahedron Lett.*, 2013, **54**, 2014.
6. M. Mittelbach and H. Junek, *Zeitschriftfuer Naturforschung, Teil B : Anorganische Chemie, Organische Chemie*, 1979, **34**, 1580.
7. A. M. El-Reddy, A. S. Ali and A. O. Ayaad, *J. Heterocycl. Chem.*, 1989, **26**, 313.
8. A. G. J. Ignacio, D. A. Meri, B. G. Maurits and C. S. J. Leopoldine, US. Patent 213703 A1, 2012.