

Article

Tin (IV) Chloride-Promoted One-Pot Synthesis of Novel Tacrine Analogues

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Abstract: A facile synthesis of potential acetylcholinesterase (AChE) inhibitors, the tacrine analogues **3a-p**, has been accomplished by direct cyclocondensation of 1-aryl-4-cyano-5-aminopyrazole with β -ketoesters using tin(IV) chloride as catalyst. The structures of all the compounds have been confirmed by IR, ^1H - and ^{13}C -NMR.

Keywords: Alzheimer's disease; tacrine; tin(IV) chloride; cyclocondensation

1. Introduction

Alzheimer's disease (AD), the most common form of dementia among the elderly, is a progressive, degenerative disorder of the brain with a loss of memory and cognition [1]. Tacrine is a reversible inhibitor of acetylcholinesterase (AChE) that was launched in 1993 as the first drug for the treatment of AD [2]. The evaluation of the clinical effects of tacrine has shown efficacy in delaying the deterioration of the symptoms of AD, but the poor selectivity of this drug for AChE has resulted in a number of side effects, specially hepatotoxicity [3], and current research is focused on developing new AChE inhibitors with improved activity and reduced adverse side effects, therefore novel tacrine analogues have been reported [4–18].

Friedlander annulation is one of the simplest and most straightforward protocols for the preparation of quinoline derivatives [19,20]. Although it has been known for more than a century, it is still a hotspot of research. Herein, we report that the Friedlander annulation of 1-aryl-4-cyano-5-

aminopyrazole with β -ketoesters using SnCl_4 as catalyst afforded the novel tacrine analogues **3a-p** in good yields.

2. Results and Discussion

The main synthetic approach to tacrine analogues is the cyclocondensation of *o*-aminonitrile derivatives with ketones using anhydrous AlCl_3 as catalyst, but that method gives low to moderate yields [4-18]. Cabrera and co-workers [21] have reported that the synthesis of 4-aminoquinolines from 2-aminobenzonitrile and β -dicarbonyl compounds could be accomplished using Lewis acids as catalysts. They found that SnCl_4 was a very effective catalyst for the preparation of the target compounds compared with other Lewis acids.

For the investigation of reaction conditions for cyclocondensation of 1-aryl-4-cyano-5-aminopyrazole with β -ketoesters, we chose the reaction of 1-phenyl-4-cyano-5-aminopyrazole (**1a**) with methyl acetoacetate as a model reaction. Because the choice of the catalyst played a crucial role, we initially studied the effect of several catalysts on the yields and found the use of anhydrous AlCl_3 , ZnCl_2 and TiCl_4 to be much less effective and tacrine analogue **3a** was obtained in less than 43% yield. Moreover, none of the product desired **3a** was obtained when we used CuCl and CuCl_2 as catalysts. However, when a mixture of 1-phenyl-4-cyano-5-aminopyrazole (**1a**) and methyl acetoacetate in toluene was stirred under reflux in the presence of SnCl_4 , the reaction was complete within 3 h and after work up, the product **3a** was obtained in 78% yield (Table 1).

Scheme 1. Cyclocondensation of 4-cyano-5-aminopyrazoles and β -ketoesters.

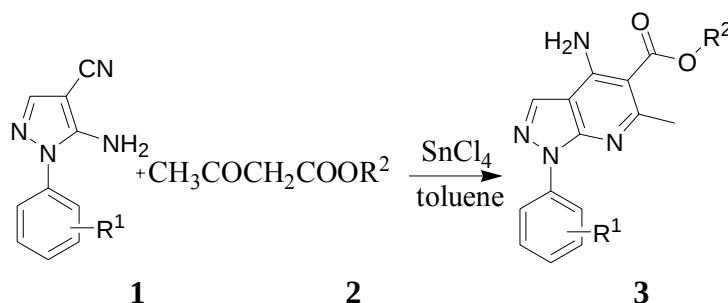


Table 1. Effect of the catalyst on the yields. ^a

Entry	Catalyst	Time(h)	Yield(%) ^b
1	CuCl	3	0
2	CuCl_2	3	0
3	AlCl_3	3	36
4	ZnCl_2	3	23
5	TiCl_4	3	43
6	SnCl_4	3	78

^a All reactions were carried out using **1a** (10 mmol), methyl acetoacetate (10 mmol), catalyst (20 mmol) and toluene (20 mL), reflux for 3 h; ^b Isolated yields.

A profound solvent effect on the reaction was observed. We initially studied the effect on the reaction of non-polar solvents, such as DCM, DCE, THF and toluene, in which SnCl_4 is easily

dissolved. Then we went on to study the polar solvent DMF. The results are summarized in Table 2. These results suggest that the solvent had a dramatic effect on the yields. Toluene was found to be the best solvent.

Table 2. Effect of the solvent on the yields. ^a

Entry	Solvent	Time (h)	Yield (%) ^b
1	DCM	3	53
2	DCE	3	68
3	THF	3	51
4	Toluene	3	78
5	DMF	3	0

^a All reactions were carried out using **1a** (10 mmol), methyl acetoacetate (10 mmol), SnCl₄ (20 mmol) and solvent (20 mL), reflux for 3 h; ^b Isolated yields.

Under the optimized reaction conditions (SnCl₄ as catalyst and anhydrous toluene as solvent, reflux for 3 h), a series of reactions between 1-aryl-4-cyano-5-aminopyrazoles and β-ketoesters were tested and a series of tacrine analogues **3** was thus prepared in good yields, regardless of the position of the group R¹ on the aromatic ring. The results were summarized in Table 3.

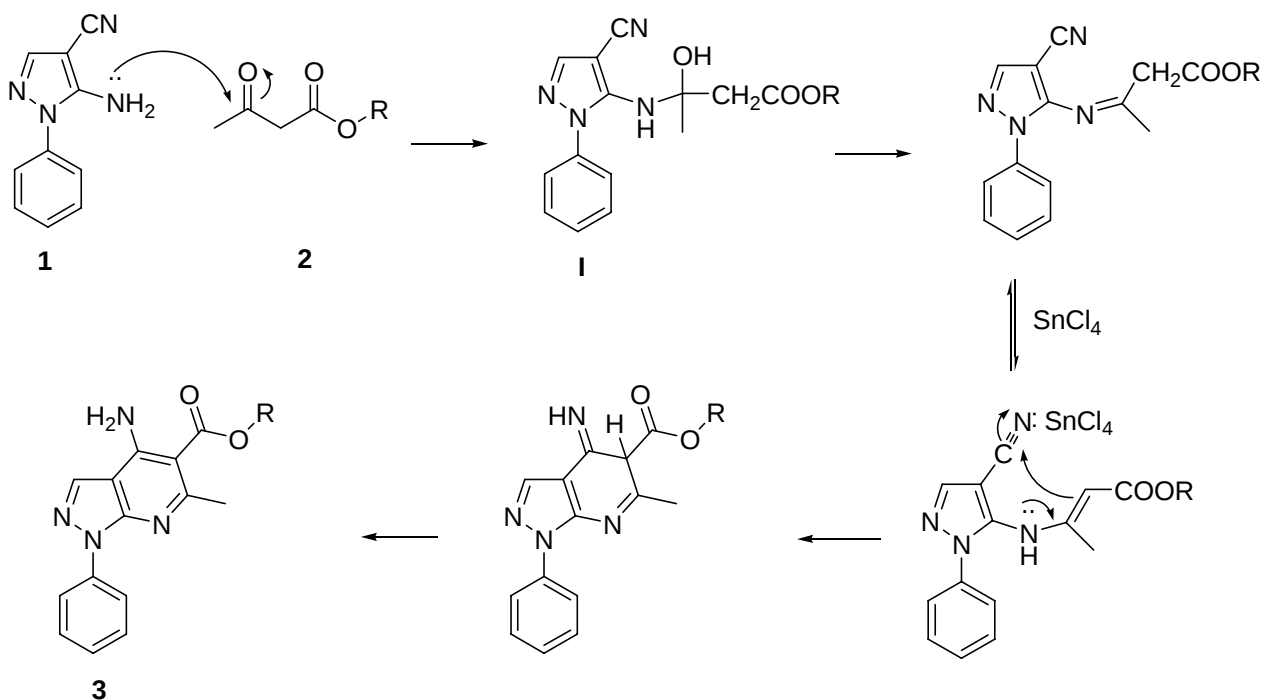
Table 3. Cyclocondensation of substituted *o*-aminobenzonitrile and β-ketoesters. ^a

Entry	R ¹	R ²	Product(3)	Yield(%) ^b
1	H	Me	3a	78
2	4-CH ₃	Me	3b	75
3	3-CH ₃	Me	3c	70
4	4-Cl	Me	3d	74
5	3-Cl	Me	3e	72
6	2-Cl	Me	3f	65
7	4-NO ₂	Me	3g	62
8	2,4-NO ₂	Me	3h	58
9	H	Et	3i	76
10	4-CH ₃	Et	3j	74
11	3-CH ₃	Et	3k	71
12	4-Cl	Et	3l	75
13	3-Cl	Et	3m	73
14	2-Cl	Et	3n	64
15	4-NO ₂	Et	3o	60
16	2,4-NO ₂	Et	3p	57

^a All reactions were carried out using **1a** (10 mmol), β-ketoesters (10 mmol), SnCl₄ (20 mmol) and toluene (20 mL), reflux for 3 h; ^b Isolated yields.

The mechanism of formation of tacrine analogue **3** can be explained by Scheme 2. The attack of the amino group of **1** onto the carbonyl carbon atom of **2** gave intermediate **I**, from which product **3** was obtained through the Friedlander reaction.

Scheme 2. Proposed mechanism.



3. Experimental

3.1. General

All melting points were determined on an XT-4A apparatus. TLC was performed using precoated silica gel GF₂₅₄ (0.25 mm), column chromatography was performed using silica gel (200–300 mesh). The ¹H- and ¹³C-NMR spectra were measured at 300 and 75 MHz, respectively, on a Bruker Advance 300 spectrometer at 25 °C, using TMS as internal standard. *J*-values are given in Hz. The IR spectra were taken on a Bruker Vector 55 spectrometer. 1-Aryl-4-cyano-5-aminopyrazoles **1** were prepared according to a reported procedure [22].

3.2. Typical procedure

1-Aryl-4-cyano-5-aminopyrazole **1** (10 mmol) and SnCl_4 (2.3 mL, 20 mmol) were added to a stirred solution of β-ketoester (10 mmol) in dry toluene (20 mL). The reaction mixture was stirred under nitrogen at room temperature for 30 min and then heated under reflux for 3 h. The reaction mixture was cooled and dispersed into water and titrated to pH 12–13 with a saturated aqueous solution of Na_2CO_3 . After filtration, the filtrate was extracted three times with ethyl acetate, the organic layers were dried and evaporated at reduced pressure to give the solid product. The product was purified by silica gel column chromatography to give **3a-p**.

*Methyl 4-amino-6-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine-5-carboxylate (3a)*. Colorless solid. m.p. 125–126 °C. ¹H-NMR (CDCl_3) δ : 8.24 (d, *J* = 6.9 Hz, 2H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.41–7.48 (m, 2H, Ar-H), 7.23–7.28 (m, 1H, Ar-H), 6.74 (br, 2H, -NH₂), 3.90 (s, 3H, -OCH₃), 2.80 (s,

3H, -CH₃). ¹³C-NMR (CDCl₃) δ: 169.9, 163.1, 151.8, 150.0, 138.7, 131.6, 128.8, 126.3, 121.6, 105.3, 101.2, 51.6, 28.1. MS-ESI (*m/z*, relative intensity, %): 285 (M⁺+3) (3), 284 (M⁺+2) (18), 283 (M⁺+1) (100). IR (KBr, cm⁻¹) ν: 3,451, 3,330 (NH₂), 3,111 (ArH), 2,976, 2,926 (CH₃), 1,665 (C=O), 1,590, 1,495, 1,460 (C=N and aromatic ring skeleton vibration), 1,260 (O-CH₃).

Methyl 4-amino-6-methyl-1-p-tolyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3b). Colorless solid. m.p. 167–168 °C. ¹H-NMR (CDCl₃) δ: 8.08 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.05 (s, 1H, pyrazole H), 7.25–7.29 (m, 2H, Ar-H), 6.74 (br, 2H, -NH₂), 3.91 (s, 3H, -OCH₃), 2.80 (s, 3H, pyridine-CH₃), 2.38 (s, 3H, benzene-CH₃). ¹³C-NMR (CDCl₃) δ: 169.2, 162.1, 151.9, 149.5, 136.3, 135.4, 130.6, 128.9, 121.0, 104.7, 100.5, 51.5, 27.9, 20.8. MS-ESI (*m/z*, relative intensity, %): 299 (M⁺+3) (3), 298 (M⁺+2) (20), 297 (M⁺+1) (100). IR (KBr, cm⁻¹) ν: 3,452, 3,333 (NH₂), 3,110 (ArH), 2,976, 2,925 (CH₃), 1,660 (C=O), 1,590, 1,495, 1,460 (C=N and aromatic ring skeleton vibration), 1,246 (O-CH₃).

Methyl 4-amino-6-methyl-1-m-tolyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3c). Colorless solid. m.p. 151–153 °C. ¹H-NMR (CDCl₃) δ: 8.07 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.33–7.39 (m, 1H, Ar-H), 7.11–7.16 (m, 1H, Ar-H), 6.72 (br, 2H, -NH₂), 3.91 (s, 3H, -OCH₃), 2.82 (s, 3H, pyridine-CH₃), 2.40 (s, 3H, benzene-CH₃). ¹³C-NMR (CDCl₃) δ: 169.0, 162.1, 151.0, 149.5, 138.6, 131.4, 128.1, 126.2, 125.1, 121.5, 118.7, 104.9, 101.0, 51.8, 28.1, 21.0. MS-ESI (*m/z*, relative intensity, %): 299 (M⁺+3) (2), 298 (M⁺+2) (22), 297 (M⁺+1) (100). IR (KBr, cm⁻¹) ν: 3,453, 3,332 (NH₂), 3,112 (ArH), 2,978, 2,923 (CH₃), 1,672 (C=O), 1,596, 1,497, 1,465 (C=N and aromatic ring skeleton vibration), 1,260 (O-CH₃).

Methyl 4-amino-1-(4-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3d). Colorless solid. m.p. 160–162 °C. ¹H-NMR (CDCl₃) δ: 8.26 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.40–7.48 (m, 2H, Ar-H), 6.72 (br, 2H, -NH₂), 3.91 (s, 3H, -OCH₃), 2.81 (s, 3H, -CH₃). ¹³C-NMR (CDCl₃) δ: 168.8, 161.7, 151.2, 135.0, 131.7, 130.6, 127.9, 121.0, 118.2, 104.9, 100.4, 51.7, 28.0. MS-ESI (*m/z*, relative intensity, %): 320 (9), 319 (32), 317 (M⁺+1) (100). IR (KBr, cm⁻¹) ν: 3,451, 3,330 (NH₂), 3,111 (ArH), 2,976, 2,926 (CH₃), 1,665 (C=O), 1,592, 1,494, 1,458 (C=N and aromatic ring skeleton vibration), 1,260 (O-CH₃).

Methyl 4-amino-1-(3-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3e). Colorless solid. m.p. 127–128 °C. ¹H-NMR (CDCl₃) δ: 8.36–8.40 (m, 1H, Ar-H), 8.27–8.31 (m, 1H, Ar-H), 8.05 (s, 1H, pyrazole H), 7.40–7.43 (m, 1H, Ar-H), 7.24–7.26 (m, 1H, Ar-H), 6.74 (br, 2H, -NH₂), 3.90 (s, 3H), 2.82 (s, 3H, -CH₃). ¹³C-NMR (CDCl₃) δ: 168.9, 161.7, 151.1, 132.7, 131.5, 130.6, 130.1, 129.6, 128.4, 125.6, 121.7, 120.8, 118.4, 51.7, 28.0. MS-ESI (*m/z*, relative intensity, %): 319 (7), 318 (33), 317 (M⁺+1) (100). IR (KBr) ν: 3,453, 3,333 (NH₂), 3,110 (ArH), 2,976, 2,924 (CH₃), 1,668 (C=O), 1,592, 1,496, 1,461 (C=N and aromatic ring skeleton vibration), 1,258 (O-CH₃).

Methyl 4-amino-1-(2-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3f). Colorless solid. m.p. 154–155 °C. ¹H-NMR (CDCl₃) δ: 8.12 (s, 1H, Ar-H), 8.05 (s, 1H, pyrazole H), 7.55–7.58 (m, 1H, Ar-H), 7.39–7.42 (m, 2H, Ar-H), 6.74 (br, 2H, -NH₂), 3.90 (s, 3H, -OCH₃), 2.80 (s, 3H, -CH₃). ¹³C-NMR (CDCl₃) δ: 169.2, 162.8, 151.4, 151.3, 135.9, 131.7, 132.1, 130.5, 129.4, 129.1,

126.4, 103.1, 100.9, 51.6, 27.9. MS-ESI (m/z , relative intensity, %): 319 (8), 318 (33), 317 ($M^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,451, 3,330 (NH_2), 3,112 (ArH), 2,975, 2,923 (CH_3), 1,665 (C=O), 1,591, 1,495, 1,458 (C=N and aromatic ring skeleton vibration), 1,262 (O-CH_3).

Methyl 4-amino-6-methyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3g). Yellowish solid. m.p. 190–192 °C. $^1\text{H-NMR}$ (DMSO) δ : 8.62–8.74 (m, 3H, Ar-H and pyrazole H), 8.37–8.40 (m, 2H, Ar-H), 7.84 (br, 2H, $-\text{NH}_2$), 3.92 (s, 3H, $-\text{OCH}_3$), 2.79 (s, 3H, $-\text{CH}_3$). $^{13}\text{C-NMR}$ (DMSO) δ : 168.0, 161.4, 151.3, 150.9, 144.6, 136.6, 125.1, 119.8, 118.5, 105.0, 102.4, 51.8, 29.0. MS-ESI (m/z , relative intensity, %): 330 ($M^+ + 3$) (3), 329 ($M^+ + 2$) (18), 328 ($M^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,451, 3,330 (NH_2), 3,111 (ArH), 2,976, 2,926 (CH_3), 1,680 (C=O), 1,610, 1,543, 1,508 (C=N and aromatic ring skeleton vibration), 1,272 (O-CH_3).

Methyl 4-amino-1-(2,4-dinitrophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3h). Yellowish solid. m.p. 202–204 °C. $^1\text{H-NMR}$ (DMSO) δ : 8.86 (s, 1H, Ar-H), 8.69–8.73 (m, 1H, Ar-H), 8.52 (s, 1H, pyrazole H), 8.41–8.45 (m, 1H, Ar-H), 7.76 (br, 2H, $-\text{NH}_2$), 3.91 (s, 3H, $-\text{OCH}_3$), 2.80 (s, 3H, $-\text{CH}_3$). $^{13}\text{C-NMR}$ (DMSO) δ : 167.8, 162.2, 151.4, 150.7, 137.4, 134.9, 128.6, 128.4, 126.3, 126.1, 126.0, 121.7, 119.5, 51.8, 28.2. MS-ESI (m/z , relative intensity, %): 375 ($M^+ + 3$) (5), 374 ($M^+ + 2$) (21), 373 ($M^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,332 (NH_2), 3,112 (ArH), 2,979, 2,933 (CH_3), 1,679 (C=O), 1,612, 1,550, 1,515 (C=N and aromatic ring skeleton vibration), 1,277 (O-CH_3).

Ethyl 4-amino-6-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3i). Colorless solid. m.p. 130–131 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 8.25 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.46–7.50 (m, 2H, Ar-H), 7.25–7.31 (m, 1H, Ar-H), 6.76 (br, 2H), 4.39 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.81 (s, 3H, $-\text{CH}_3$), 1.42 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 169.2, 162.5, 151.4, 150.2, 139.4, 131.7, 128.9, 126.1, 121.4, 105.1, 101.5, 60.7, 28.4, 14.3. MS-ESI (m/z , relative intensity, %): 299 ($M^+ + 3$) (3), 298 ($M^+ + 2$) (19), 297 ($M^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,333 (NH_2), 3,110 (ArH), 2,976, 2,926 (CH_2 and CH_3), 1,665 (C=O), 1,592, 1,494, 1,460 (C=N and aromatic ring skeleton vibration), 1,260 (O-CH_3).

Ethyl 4-amino-6-methyl-1-p-tolyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3j). Colorless solid. m.p. 173–174 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 8.09 (d, $J = 6.6$ Hz, 2H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.25–7.29 (m, 2H, Ar-H), 6.72 (br, 2H, $-\text{NH}_2$), 4.40 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.81 (s, 3H, pyridine- CH_3), 2.39 (s, 3H, benzene- CH_3), 1.43 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). $^{13}\text{C-NMR}$ (CDCl_3) δ : 168.9, 162.0, 151.0, 149.7, 136.5, 135.5, 130.9, 129.1, 121.1, 104.5, 100.9, 60.3, 28.0, 20.6, 13.9. MS-ESI (m/z , relative intensity, %): 313 ($M^+ + 3$) (2.5), 312 ($M^+ + 2$) (22), 311 ($M^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,335 (NH_2), 3,112 (ArH), 2,977, 2,930 (CH_2 and CH_3), 1,658 (C=O), 1,590, 1,492, 1,460 (C=N and aromatic ring skeleton vibration), 1,260 (O-CH_3).

Ethyl 4-amino-6-methyl-1-m-tolyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3k). Colorless solid. m.p. 148–149 °C. $^1\text{H-NMR}$ (CDCl_3) δ : 8.08 (d, $J = 8.7$ Hz, 2H, Ar-H), 8.01 (s, 1H, pyrazole H), 7.38 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.11 (d, $J = 7.5$ Hz, 1H, Ar-H), 6.72 (br, 2H, $-\text{NH}_2$), 4.40 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.82 (s, 3H, pyridine- CH_3), 2.45 (s, 3H, benzene- CH_3), 1.43 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$).

^{13}C -NMR (CDCl_3) δ : 168.8, 162.1, 150.9, 149.6, 138.5, 131.1, 128.3, 126.6, 125.6, 121.7, 118.3, 104.6, 101.1, 60.4, 28.0, 21.2, 13.9. MS-ESI (m/z , relative intensity, %): 313 ($\text{M}^+ + 3$) (2), 312 ($\text{M}^+ + 2$) (20), 311 ($\text{M}^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,336 (NH_2), 3,111 (ArH), 2,976, 2,926 (CH_2 and CH_3), 1,662 ($\text{C}=\text{O}$), 1,590, 1,494, 1,462 ($\text{C}=\text{N}$ and aromatic ring skeleton vibration), 1,262 ($\text{O}-\text{CH}_3$).

Ethyl 4-amino-1-(4-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3l). Colorless solid. m.p. 143–144 °C. ^1H -NMR (CDCl_3) δ : 8.27 (d, $J = 6.6$ Hz, 2H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.43–7.49 (m, 2H, Ar-H), 6.74 (br, 2H, $-\text{NH}_2$), 4.40 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.81 (s, 3H, $-\text{CH}_3$), 1.43 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). ^{13}C -NMR (CDCl_3) δ : 168.9, 162.0, 151.0, 135.3, 131.6, 130.9, 128.1, 121.1, 118.5, 104.5, 100.9, 60.3, 28.0, 13.9. MS-ESI (m/z , relative intensity, %): 334 (8), 333 (33), 331 ($\text{M}^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,338 (NH_2), 3,113 (ArH), 2,973, 2,925 (CH_2 and CH_3), 1,660 ($\text{C}=\text{O}$), 1,593, 1,457 ($\text{C}=\text{N}$ and aromatic ring skeleton vibration), 1,260 ($\text{O}-\text{CH}_3$).

Ethyl 4-amino-1-(3-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3m). Colorless solid. m.p. 105–106 °C. ^1H -NMR (CDCl_3) δ : 8.37–8.42 (m, 1H, Ar-H), 8.28–8.33 (m, 1H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.41–7.46 (m, 1H, Ar-H), 7.23–7.27 (m, 1H, Ar-H), 6.73 (br, 2H, $-\text{NH}_2$), 4.41 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.83 (s, 3H, $-\text{CH}_3$), 1.44 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). ^{13}C -NMR (CDCl_3) δ : 168.7, 161.9, 150.9, 132.9, 131.6, 130.6, 130.2, 129.5, 128.6, 125.4, 121.8, 120.6, 118.5, 60.4, 27.9, 13.8. MS-ESI (m/z , relative intensity, %): 334 (6), 333 (31), 331 ($\text{M}^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,337 (NH_2), 3,111 (ArH), 2,974, 2,928 (CH_2 and CH_3), 1,661 ($\text{C}=\text{O}$), 1,592, 1,490, 1,458 ($\text{C}=\text{N}$ and aromatic ring skeleton vibration), 1,258 ($\text{O}-\text{CH}_3$).

Ethyl 4-amino-1-(2-chlorophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3n). Colorless solid. m.p. 164–165 °C. ^1H -NMR (CDCl_3) δ : 8.11 (s, 1H, Ar-H), 8.04 (s, 1H, pyrazole H), 7.51–7.57 (m, 1H, Ar-H), 7.38–7.42 (m, 2H, Ar-H), 6.83 (br, 2H, $-\text{NH}_2$), 4.40 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.72 (s, 3H), 1.41 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). ^{13}C -NMR (CDCl_3) δ : 168.8, 162.5, 151.1, 150.9, 135.4, 131.9, 131.8, 130.2, 129.6, 129.4, 126.9, 103.4, 101.2, 60.3, 27.7, 13.9. MS-ESI (m/z , relative intensity, %): 334 (5), 333 (32), 331 ($\text{M}^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,338 (NH_2), 3,112 (ArH), 2,973, 2,930 (CH_2 and CH_3), 1,660 ($\text{C}=\text{O}$), 1,590, 1,493, 1,457 ($\text{C}=\text{N}$ and aromatic ring skeleton vibration), 1,263 ($\text{O}-\text{CH}_3$).

Ethyl 4-amino-6-methyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3o). Yellowish solid. m.p. 197–199 °C. ^1H -NMR (DMSO) δ : 8.62–8.74 (m, 3H, Ar-H and pyrazole H), 8.36–8.41 (m, 2H, Ar-H), 7.84 (br, 2H, $-\text{NH}_2$), 4.32 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.67 (s, 3H, $-\text{CH}_3$), 1.33 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). ^{13}C -NMR (DMSO) δ : 167.8, 161.2, 151.0, 150.5, 144.4, 136.3, 124.9, 119.6, 118.9, 105.4, 102.6, 60.6, 29.3, 14.2. MS-ESI (m/z , relative intensity, %): 344 ($\text{M}^+ + 3$) (2.5), 343 ($\text{M}^+ + 2$) (18), 342 ($\text{M}^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,333 (NH_2), 3,112 (ArH), 2,978, 2,930 (CH_2 and CH_3), 1,678 ($\text{C}=\text{O}$), 1,616, 1,545, 1,512 ($\text{C}=\text{N}$ and aromatic ring skeleton vibration), 1,275 ($\text{O}-\text{CH}_3$).

Ethyl 4-amino-1-(2,4-dinitrophenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (3p). Yellowish solid. m.p. 205–206 °C. ^1H -NMR (DMSO) δ : 8.86 (s, 1H, Ar-H), 8.69–8.73 (m, 1H, Ar-H), 8.52 (s, 1H, pyrazole H), 8.43 (d, $J = 9.0$ Hz, 1H, Ar-H), 7.74 (br, 2H, $-\text{NH}_2$), 4.39 (q, $J = 7.2$ Hz, 2H, $-\text{CH}_2\text{CH}_3$), 2.67 (s, 3H, $-\text{CH}_3$), 1.33 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$).

CH_2CH_3), 2.66 (s, 3H, $-\text{CH}_3$), 1.39 (t, $J = 7.2$ Hz, 3H, $-\text{CH}_2\text{CH}_3$). ^{13}C -NMR (DMSO) δ : 167.8, 162.2, 151.4, 150.7, 137.4, 134.9, 128.6, 128.4, 126.3, 126.1, 126.0, 121.7, 119.5, 60.2, 27.9, 14.0. MS-ESI (m/z , relative intensity, %): 389 ($\text{M}^+ + 3$) (4), 388 ($\text{M}^+ + 2$) (19), 387 ($\text{M}^+ + 1$) (100). IR (KBr, cm^{-1}) ν : 3,453, 3,331 (NH_2), 3,113 (ArH), 2,979, 2,932 (CH_2 and CH_3), 1,680 ($\text{C}=\text{O}$), 1,617, 1,545, 1,512 ($\text{C}=\text{N}$ and aromatic ring skeleton vibration), 1,272 ($\text{O}-\text{CH}_3$).

4. Conclusions

We have developed an efficient catalyst system using SnCl_4 in anhydrous toluene for the reaction between *o*-aminonitriles containing pyrazole moieties with β -ketoesters. A series of novel tacrine analogues **3a-p** has been thus synthesized and their spectroscopic characterization and structural features have been presented.

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Sample Availability: Samples of compounds **3a-p** are available from the authors.

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