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Article

Microwave-Assisted Synthesis of Indole-2-Carboxylic Acid Esters in Ionic Liquid

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Um procedimento melhorado para a síntese de ésteres ácido indol-2-acético em rendimentos excelentes foi obtido pela condensação de 2-halo aril aldeídos ou cetonas e isocianoacetato de etila usando líquido iônico sob irradiação de microondas controlada (100 W) a 50 ºC. Este método oferece um número de vantagens em termos de metodologia simples, com rendimento elevado num tempo de reação curto e em condições de reação amenas.

An improved procedure for the synthesis of indole-2-carboxylic acid esters in excellent yields has been achieved by the condensation of 2-halo aryl aldehydes or ketones and ethyl isocyanoacetate using ionic liquid under controlled microwave irradiation (100 W) at 50 °C. This method offers a number of advantages in terms of methodology, high-product yield, short period of conversion, mild reaction conditions and easy workup.

Keywords: indole, synthesis, ionic liquid, microwave irradiation

Introduction

The indole moiety is a vital structural unit found in a large array of natural products and pharmaceuticals. Consequently, synthetic approaches toward indoles have attracted significant attention.[1-3] In many cases, the well-studied Fischer indole synthesis is the method of choice, but this approach suffers from problems such as low yield and formation of side products.[4] In our design of new inhibitors of aspartyl protease,[5,6] we were interested in differently substituted indole-2-carboxylic acid esters. Owing to their structural diversity and remarkable biological functions, a multitude of methods exist for the synthesis of these compounds. The conventional method is the Hemetsberger-Knittel indole synthesis.[7] This method involves the condensation between an arylaldehyde and an azidoacetate to provide *a*-azidocinnamates which upon heating give indoles. One problem is associated with employing high boiling solvents such as mesitylene, xylene and toluene.[8,9] In addition, the yield of the reaction is low.[10] Cai and co-workers[11] developed a copper-catalyzed cascade process from 2-halo aryl aldehydes/ketones with isocyanoacetate for synthesis of these derivatives. However, the procedure has some drawbacks such as long reaction time and moderate yields. For the cyclization of 2-chloro aryl aldehydes/ketones with isocyanoacetate, the yield of the reaction is unsatisfactory and the temperature of the reaction is high. Therefore, it is necessary to develop a more practical method for synthesis of such a significant scaffold.

The research and application of green chemistry principles have led to the development of cleaner processes. Since the start of this century an ever-growing number of studies has been published describing the use of ionic liquids.[12-17] Microwave-assisted organic synthesis has shown to be a valuable tool for reducing reaction times, getting cleaner reactions, improving yields, simplifying workup and designing energy-saving protocols.[18,19]

Due to their ionic nature, ionic liquids allow highly effective interactions with microwave energy for the rapid generation of products with generally high yields.[20] Herein, we developed a fast and practical method for the synthesis of indole-2-carboxylic acid esters in the presence of 1-methyl-3-butylimidazolium hydroxide ([bmim]OH) under controlled microwave irradiation (100 W) at 50 °C. The synthetic sequence is depicted in Scheme 1.

Results and Discussion

Initial studies were carried out using 2-bromo benzenealdehyde as the substrate and isocyanoacetate as

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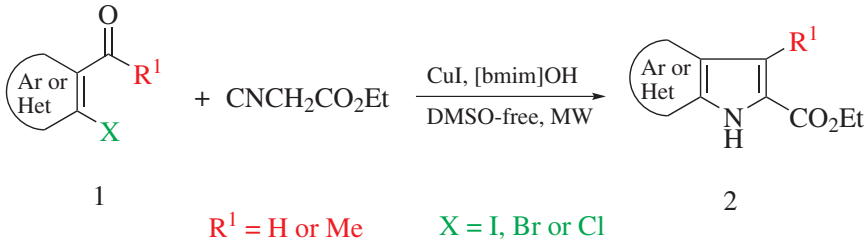


Scheme 1. Sequence for the synthesis of indole-2-carboxylic acid esters in the presence of 1-methyl-3-butylimidazolium hydroxide ([bmim]OH) under controlled microwave irradiation.

the nitrogen source in [bmim]OH under the catalysis of CuI (12 mol%) for 8 h, the desired product ethyl 1*H*-indole-2-carboxylate was obtained in moderate yield (57%). When the reaction was irradiated under controlled microwave (100 W) for 10 min at 50 °C, 91% of the desired product was reached. Encouraged by the result, other Cu reagents, such as CuBr or CuCl, were investigated in the presence of [bmim]OH under microwave irradiation. The results showed that replacement of CuI with CuBr slightly affected the outcome of this reaction (entry 1 and entry 9, Table 1). CuCl was less active (entries 9-10, Table 1). When other copper sources such as Cu_2O and $Cu(OAc)_2$ were used, no desired product was detected.

Next, the reaction time and the temperature were investigated in order to find the optimal reaction conditions. It was found that 10 min was long enough to run the reaction. Raising the reaction temperature did not obviously improve the reaction yield (entries 11-12, Table 1). Also an extended reaction time has no effect on the conversion. Finally, the optimal conditions for parallel synthesis were determined to be 12 mol% CuI at 50 °C for 10 min. The substrate variation was then investigated. To our satisfaction, the reaction shows a wide scope for the structural variations of aryl aldehydes or ketones under the optimized reaction conditions. Both electron-donating and electron-withdrawing groups allowed smooth transformation of aryl aldehydes or ketones into the corresponding products with high yields. Performing the reaction with 2-chloro aryl aldehydes or ketones gave good yields (entries 13-16, Table 1). It was noteworthy that hetero-aryl aldehydes or ketones with varied substitutions were found to undergo the reaction (entries 17-20, Table 1). It was found that DMSO-free condition gave the corresponding product in excellent yield (entries 21-24, Table 1). To illustrate the preparative utility, our procedure was performed on a large scale (entry 25, Table 1). A 60-mmol-scale synthesis gave the desired product in 88% yield.

Conclusions

In summary, in this study we have successfully extended the use of ionic liquid [bmim]OH under microwave irradiation for assembly of indole-2-carboxylic acid esters in high yields. The experimental procedure is very simple and the reaction time is short. The synthetic protocols described above have proven amenable to scale-up to over 10-g quantities.

Experimental

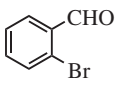
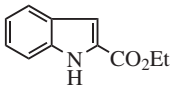
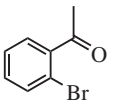
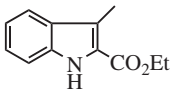
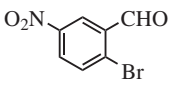
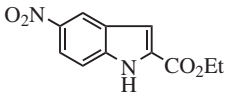
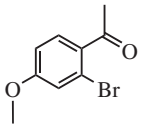
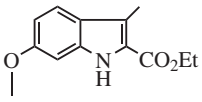
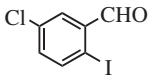
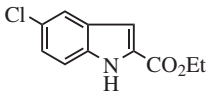
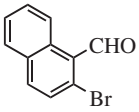
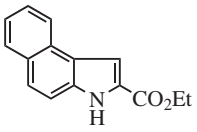
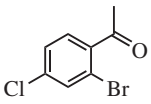
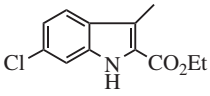
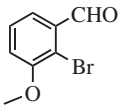
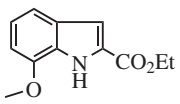
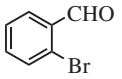
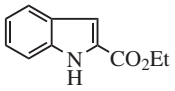
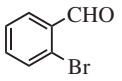
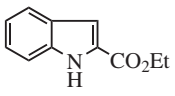
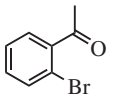
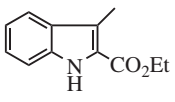
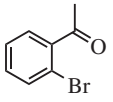
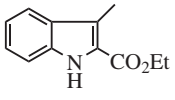
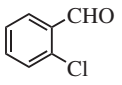
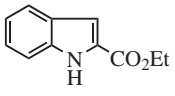
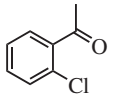
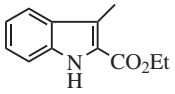
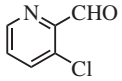
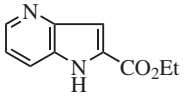
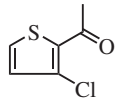
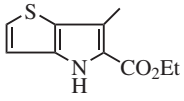
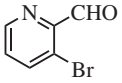
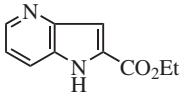
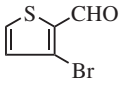
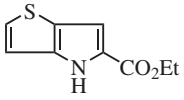
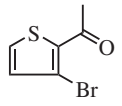
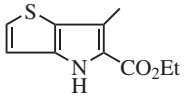
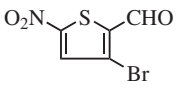
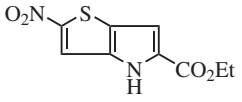
General

Reagents were obtained commercially and used as received. Solvents were purified and dried by standard methods. [bmim]OH was synthesized according to the method described in the literature.[21] Microwave reactions were performed on a CEM Explorer Hybrid 12 Discover, with built in temperature/pressure probes and associated software. The melting points (mp) were determined on an XT-4 micro melting point apparatus and uncorrected. Infrared (IR) spectra were recorded on an EQUINOX-55 spectrometer on a KBr matrix. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on an INOVA-400 NMR spectrometer using TMS as an internal standard. Chemical shift values (δ) are given in ppm. Elemental analyses were performed on a Vario EL III CHNS analyzer. Electrospray mass spectra were obtained with an MALDI-TOF Mass spectrometer. 200-300 mesh silica gel was used for column chromatography.

Representative procedure for the synthesis of 2

An oven-dried 10-mL microwave vial was charged with copper(I) iodide (0.24 mmol), [bmim]OH (2 mL), aldehydes or ketones (1 mmol), ethyl isocyanoacetate (1.1 mmol), DMSO (1 mL), or DMSO-free with the addition of a stirred bar. The reaction vessel was sealed, evacuated and flushed with argon three times. The mixture was irradiated by 100 W microwave at 50 °C for 10 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product. The crude product

Table 1. Reactions of 2-halo aryl aldehydes or ketones with ethyl isocyanoacetate[a]

entry	Substrate	Product	Yield / %[b]
1			91
2			95
3			93
4			92
5			91
6			95
7			93
8			91
9[c]			90
10[d]			58
11[e]			95
12[f]			97
13[g]			71
14[g]			74
15[g]			78
16[g]			81
17			88
18			90
19			93
20			91
21[h]			90
22[h]			93
23[h]			90
24[h]			89
25[i]			88

[a]Reaction conditions: CuI (0.24 mmol), [bmim]OH (2 mL), aryl bromides (1 mmol), ethyl isocyanoacetate (1.1 mmol), DMSO (1 mL), Ar atmosphere, microwave irradiation, 50 °C, 10 min; [b]isolated yields; [c]CuBr as catalyst; [d]CuCl as catalyst; [e]reaction temperature of 60 °C; [f]reaction temperature of 70 °C; [g]reaction temperature of 60 °C; [h]without DMSO; [i]CuI (15 mmol), [bmim]OH (35 mL), aryl bromides (60 mmol), ethyl isocyanoacetate (66 mmol), Ar atmosphere, microwave irradiation, 50 °C.

was purified by flash chromatography with ethyl acetate/petroleum ether as eluent on silica gel to afford the desired product.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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Supplementary Information

Microwave-Assisted Synthesis of Indole-2-Carboxylic Acid Esters in Ionic Liquid

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Ethyl 1H-indole-2-carboxylate

White solid; mp 120-122 °C (lit.[1] mp 121-123 °C); IR (KBr) ν_{max}/cm^{-1} 3463, 3431, 2929, 1711 and 1695; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, 3H, *J* 6.8 Hz), 4.39 (q, 2H, *J* 6.8 Hz), 7.23-7.16 (m, 1H), 7.29-7.33 (m, 2H), 7.49-7.56 (m, 1H), 7.69 (d, 1H, *J* 9.6 Hz), 9.41 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 135.4, 128.2, 126.5, 122.6, 121.7, 121.1, 110.6, 109.2, 62.3, 14.7; MALDI-TOF MS *m/z* 189 (M^+); Anal. calcd. for $C_{11}H_{11}NO_2$: C 69.83, H 5.86, N 7.40; found: C 70.01, H 5.69, N 7.21.

Ethyl 3-methyl-1H-indole-2-carboxylate

White solid; mp 132-134 °C (lit.[2] mp 134-136 °C); IR (KBr) ν_{max}/cm^{-1} 3466, 3429, 2928, 1716 and 1691; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (t, 3H, *J* 9.6 Hz), 2.61 (s, 3H), 4.33 (q, 2H, *J* 9.6 Hz), 7.21-7.25 (m, 1H), 7.31-7.39 (m, 2H), 7.61 (d, 1H, *J* 8.0 Hz), 9.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 136.1, 128.7, 125.6, 123.7, 121.3, 120.4, 119.2, 110.5, 61.2, 14.8, 10.3; MALDI-TOF MS *m/z* 203 (M^+); Anal. calcd. for $C_{12}H_{13}NO_2$: C 70.92, H 6.45, N 6.89; found: C 71.14, H 6.49, N 6.92.

Ethyl 5-nitrol-1H-indole-2-carboxylate

Yellow solid; mp 221-223 °C (lit.[3] mp 220-222 °C); IR (KBr) ν_{max}/cm^{-1} 3460, 3431, 2931, 1506 and 1341; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, 3H, *J* 4.0 Hz), 4.38 (q, 2H, *J* 4.0 Hz), 7.41 (s, 1H), 7.59 (d, 1H, *J* 4.0 Hz), 8.11 (d, 1H, *J* 8.0 Hz), 8.63 (s, 1H), 10.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.4, 146.3, 138.9, 131.1, 125.8, 120.7, 119.5, 112.2, 110.6, 61.7, 14.3; MALDI-TOF MS *m/z* 234 (M^+); Anal. calcd. for $C_{11}H_{10}N_2O_4$: C 56.41, H 4.30, N 11.96; found: C 56.53, H 4.39, N 11.74.

Ethyl 6-methoxyl-3-methyl-1H-indole-2-carboxylate

Brown solid; mp 121-123 °C (lit.[4] mp 122-124 °C); IR (KBr) ν_{max}/cm^{-1} 3467, 3336, 2990, 1706 and 1681; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (t, 3H, *J* 7.2 Hz), 2.59 (s, 3H), 3.81 (s, 3H), 4.42 (q, 2H, *J* 7.2 Hz), 6.83 (d, 1H, *J* 2.4 Hz), 6.91-7.03 (m, 1H), 7.49 (d, 1H, *J* 8.0 Hz), 9.06 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 144.1, 130.6, 128.4, 127.0, 121.3, 118.5 109.7, 105.2, 61.7, 56.2, 14.1, 11.6; MALDI-TOF MS *m/z* 233 (M^+); Anal. calcd. for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N 6.00; found: C 66.81, H 6.44, N 6.03.

Ethyl 5-chloro-1H-indole-2-carboxylate

White solid; mp 169-171 °C (lit.[1] mp 167-169 °C); IR (KBr) ν_{max}/cm^{-1} 3461, 3343, 2928, 1715 and 1693; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, 3H, *J* 4.8 Hz), 4.41 (q, 2H, *J* 4.8 Hz), 7.31 (s, 1H), 7.41-7.44 (m, 1H), 7.53 (d, 1H, *J* 3.2 Hz), 7.67 (s, 1H), 9.89 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 137.1, 129.4, 128.6, 127.2, 122.8, 120.7, 111.5, 109.3, 62.4, 14.5; MALDI-TOF MS *m/z* 223 (M^+); Anal. calcd. for $C_{11}H_{10}ClNO_2$: C 59.07, H 4.51, N 6.26; found: C 59.16, H 4.57, N 6.32.

Ethyl 3H-benz[e]indole-2-carboxylate

Brown solid; mp 164-166 °C (lit.[5] mp 164-165 °C); IR (KBr) ν_{max}/cm^{-1} 3464, 3340, 2929, 1710 and 1691; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (t, 3H, *J* 6.0 Hz), 4.43 (q, 2H, *J* 6.0 Hz), 7.33-7.51 (m, 4H), 7.66-7.79 (m, 2H), 8.03 (d, 1H, *J* 8.0 Hz), 9.92 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.4, 135.2, 130.1, 129.0, 128.6, 127.7, 126.5, 124.8,124.1, 122.9, 121.6, 112.3, 109.1, 61.8, 14.2; MALDI-TOF MS *m/z* 239 (M^+); Anal. calcd. for $C_{15}H_{13}NO_2$: C 75.30, H 5.48, N 5.85; found: C 75.42, H 5.51, N 5.83.

Ethyl 6-chloro-3-methyl-1H-indole-2-carboxylate

White solid; mp 159-161 °C (lit.[6] mp 159-160 °C); IR (KBr) ν_{max}/cm^{-1} 3460, 3339, 2929, 1710 and 1691; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, 3H, *J* 8.0 Hz), 2.59 (s, 3H), 4.31 (q, 2H, *J* 8.0 Hz), 7.11-713 (m, 1H), 7.31-7.35 (d, 1H, *J* 1.8 Hz), 7.59 (d, 1H, *J* 9.6 Hz), 9.09

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(br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 137.2, 130.1, 128.4, 125.6, 122.5, 121.3, 120.5, 110.2, 61.3, 14.9, 9.7; MALDI-TOF MS *m/z* 237 (M^+); Anal. calcd. for $C_{12}H_{12}ClNO_2$: C 60.64, H 5.09, N 5.89; found: C 60.33, H 5.02, N 5.97.

Ethyl 7-methoxyl-1H-indole-2-carboxylate

White solid; mp 159-161 °C (lit.[1] mp 160-162 °C); IR (KBr) ν_{max}/cm^{-1} 3465, 3335, 2930, 1711 and 1695; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, *J* 6.0 Hz, 3H), 3.83 (s, 3H), 4.41 (q, 2H, *J* 6.0 Hz), 6.87 (s, 1H), 7.01-7.09 (m, 1H), 7.25 (d, 1H, *J* 2.0 Hz), 7.29 (d, 1H, *J* 7.2 Hz), 9.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 145.2, 130.2, 129.1, 128.8, 122.3, 118.6, 111.0, 105.4, 61.7, 56.2, 14.4; MALDI-TOF MS *m/z* 219 (M^+); Anal. calcd. for $C_{12}H_{13}NO_3$: C 65.74, H 5.98, N 6.39; found: C 65.69, H 5.91, N 6.44.

Ethyl 1H-pyrrolo[3,2-b]pyridine-2-carboxylate

Brown solid; mp 179-181 °C (lit.[7] mp 179 °C); IR (KBr) ν_{max}/cm^{-1} 3405, 3300, 2887 and 1685; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, 3H, *J* 7.2 Hz), 4.35 (q, 2H, *J* 7.2 Hz), 7.19 (d, 1H, *J* 7.2 Hz), 7.27 (dd, 1H, *J* 4.8, 8.1 Hz), 7.79 (d, 1H, *J* 7.2 Hz), 8.37-8.41 (m, 1H), 9.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 142.5, 141.7, 131.2, 130.1, 121.4, 120.6, 108.5, 61.1, 14.8; MALDI-TOF MS *m/z* 190 (M^+); Anal. calcd. for $C_{10}H_{10}N_2O_2$: C 63.15, H 5.30, N 14.73; found: C 63.01, H 5.37, N 14.81.

Ethyl thieno[3,2-b]pyrrole-5-carboxylate

White solid; mp 132-134 °C (lit.[8] mp 132.5-133 °C); IR (KBr) ν_{max}/cm^{-1} 3400, 3315, 2893 and 1693; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 3H, *J* 7.1 Hz), 4.30 (q, 2H, *J* 7.1 Hz), 7.0 (d, 1H, *J* 2.4 Hz), 7.18 (d, 1H, *J* 2.4 Hz), 7.26 (d, 1H, *J* 3.2 Hz), 9.31 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 131.7, 130.0, 125.1, 122.4, 118.3, 109.2, 61.7, 14.1; MALDI-TOF MS *m/z* 195 (M^+); Anal. calcd. for $C_9H_9NO_2S$: C 55.37, H 4.65, N 7.17, S 16.42; found: C 55.41, H 4.57, N 7.21, S 16.33.

Ethyl 6-methyl-thieno[3,2-b]pyrrole-5-carboxylate

White solid; mp 144-146 °C (lit.[8] mp 144-145 °C); IR (KBr) ν_{max}/cm^{-1} 3430, 3300, 2993 and 1687; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 3H, *J* 7.2 Hz), 2.43 (s, 3H), 4.31 (q, 2H, *J* 7.2 Hz), 6.69 (d, 1H, *J* 5.4 Hz), 7.31 (d, 1H, *J* 5.4 Hz), 9.42 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.8, 140.4, 130.6, 127.2, 122.9, 121.3, 109.6, 61.5, 14.8, 11.7; MALDI-TOF MS *m/z* 209 (M^+); Anal. calcd. for $C_{10}H_{11}NO_2S$: C 57.39, H 5.30, N 6.69, S 15.32; found: C 57.27, H 5.38, N 6.57, S 15.26.

Ethyl 2-nitrothieno[3,2-b]pyrrole-5-carboxylate

Yellow solid; mp 187-189 °C (lit.[9] mp 188-189 °C); IR (KBr) ν_{max}/cm^{-1} 3410, 3303, 1689, 1490 and 1370; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (t, 3H, *J* 7.0 Hz), 4.33 (q, 2H, *J* 7.0 Hz), 7.11 (m, 1H), 7.76 (d, 1H, *J* 4.8 Hz), 9.39 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 151.3, 137.4, 131.6, 128.1, 122.2, 108.5, 60.6, 14.1; MALDI-TOF MS *m/z* 240 (M^+); Anal. calcd. for $C_9H_8N_2O_4S$: C 45.00, H 3.36, N 11.66, S 13.35; found: C 45.06, H 3.38, N 11.59, S 13.29.

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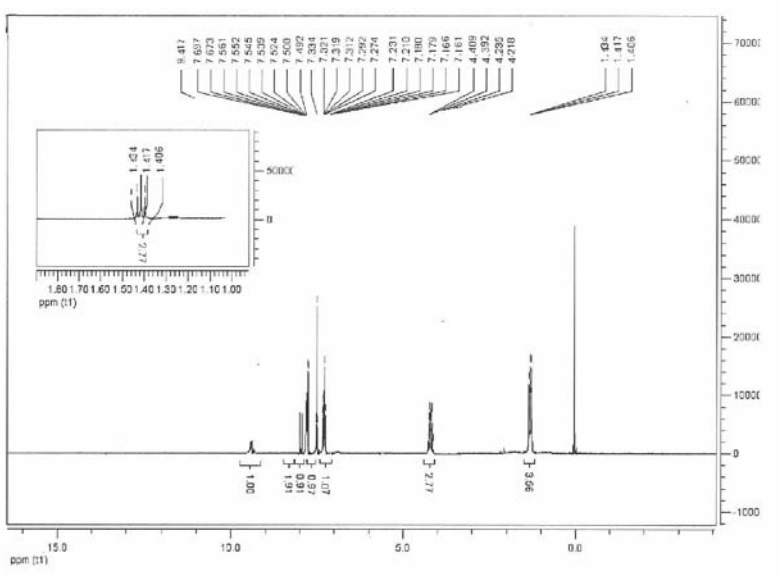

Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 1*H*-indole-2-carboxylate.

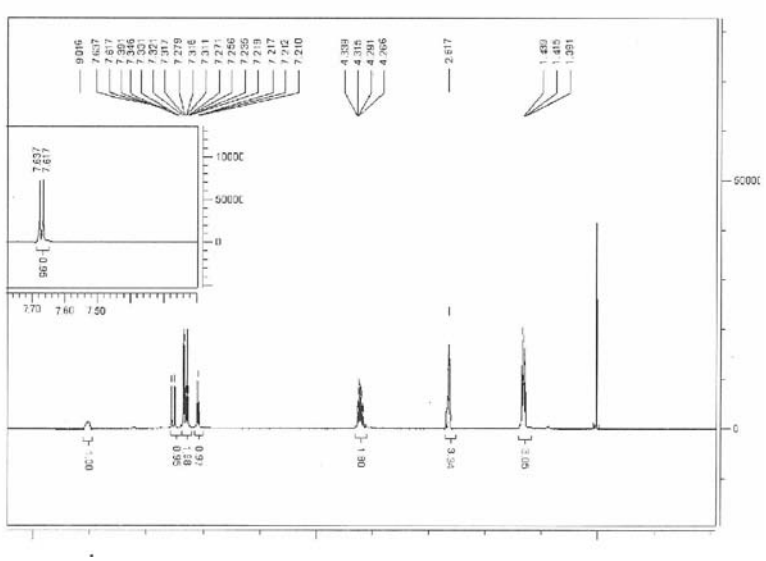

Figure S2. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 3-methyl-1*H*-indole-2-carboxylate.

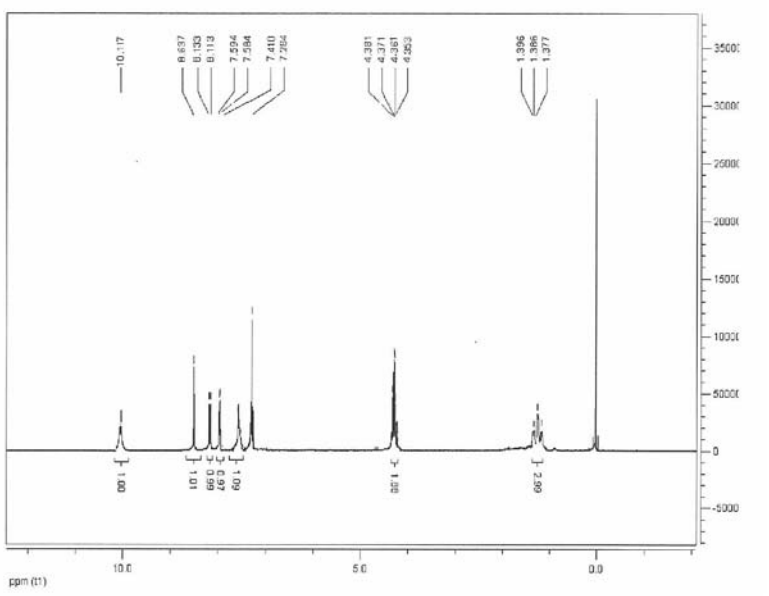

Figure S3. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 5-nitrol-1*H*-indole-2-carboxylate.

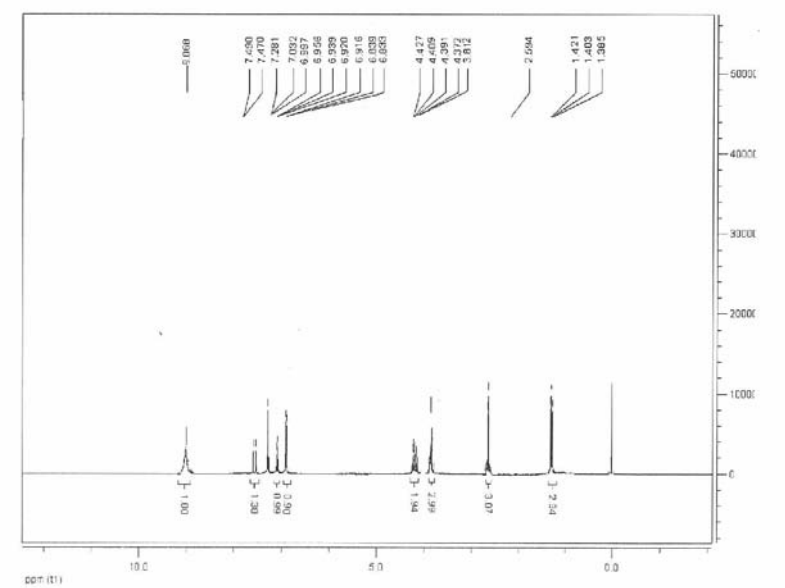

Figure S4. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 6-methoxyl-3-methyl-1*H*-indole-2-carboxylate.

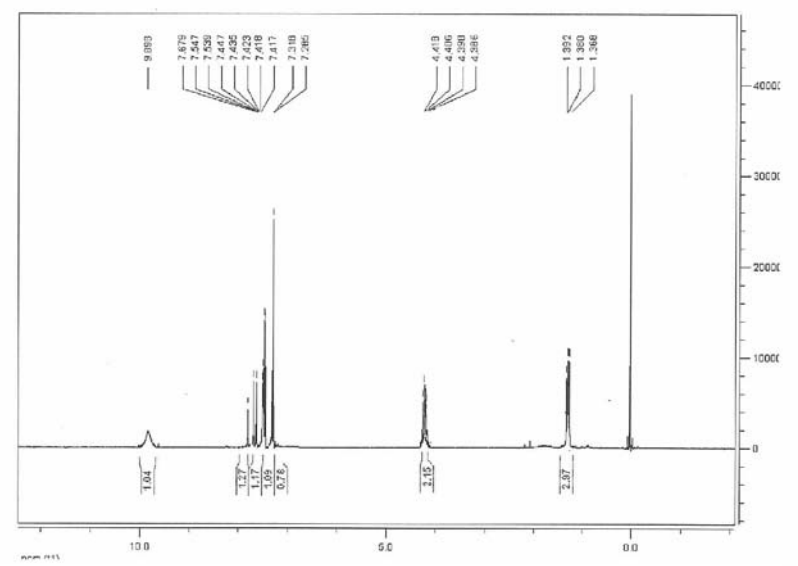

Figure S5. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 5-chloro-1*H*-indole-2-carboxylate.

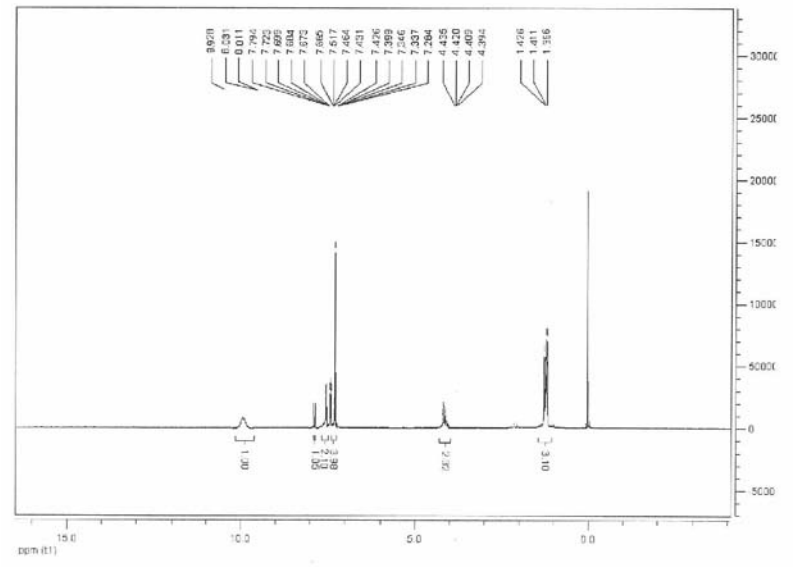

Figure S6. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 3*H*-benz[e]indole-2-carboxylate.

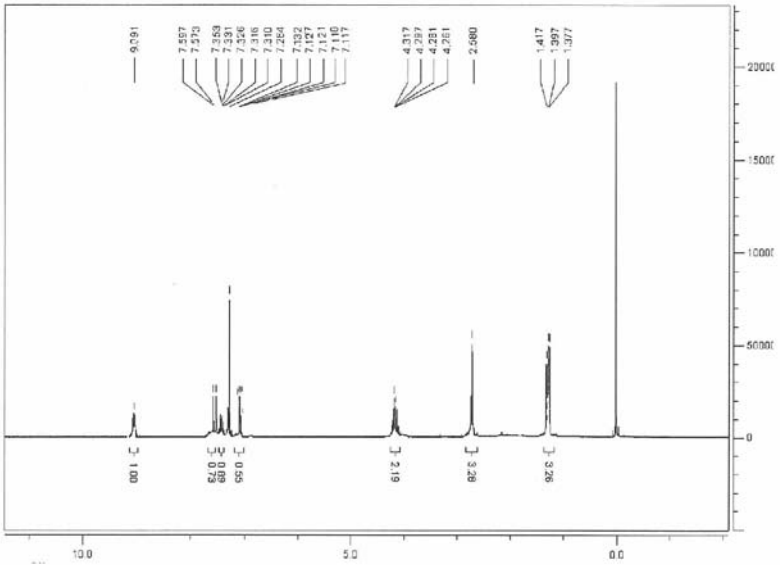

Figure S7. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 6-chloro-3-methyl-1*H*-indole-2-carboxylate.

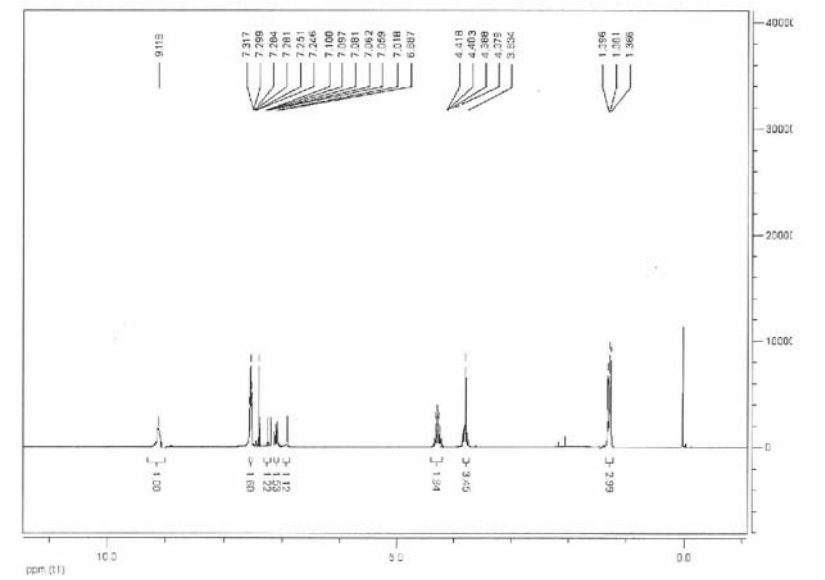

Figure S8. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 7-methoxyl-1*H*-indole-2-carboxylate.

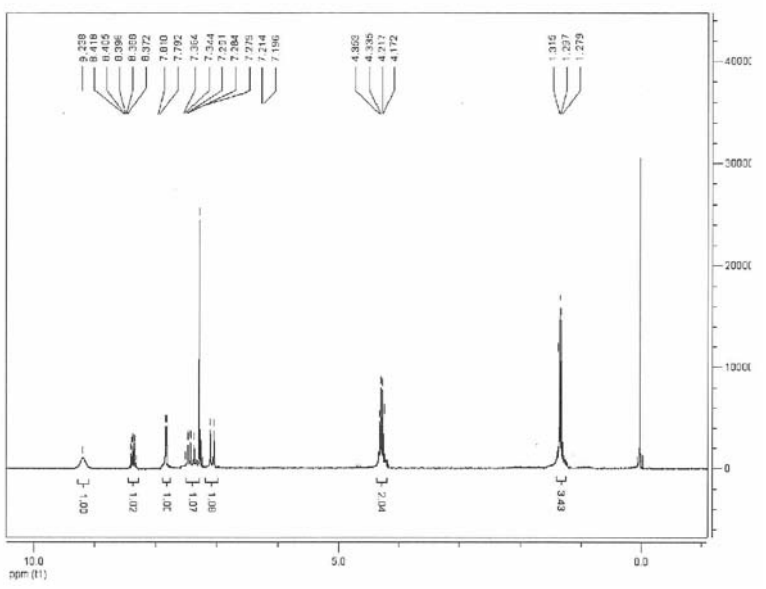

Figure S9. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 1*H*-pyrrolo[3,2-b]pyridine-2-carboxylate.

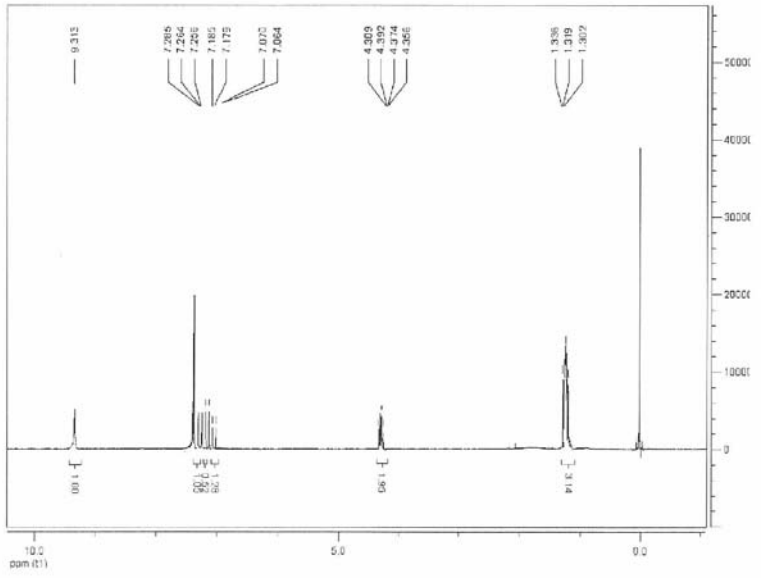

Figure S10. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl thieno[3,2-b]pyridine-5-carboxylate.

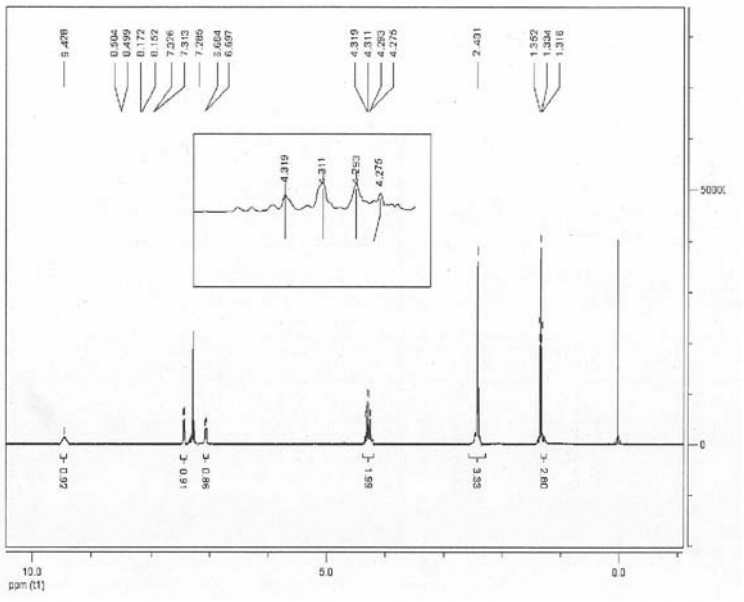

Figure S11. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 6-methyl-thieno[3,2-b]pyrrole-5-carboxylate.

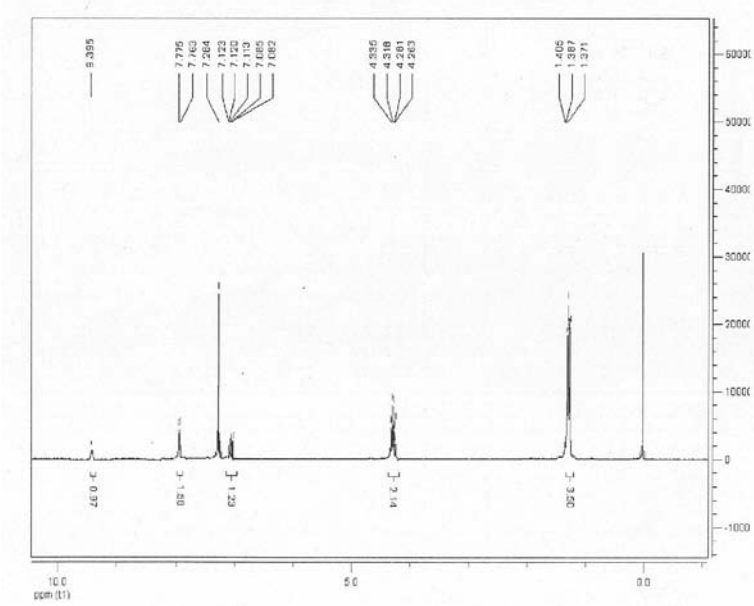

Figure S12. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of ethyl 2-nitrothieno[3,2-b]pyrrole-5-carboxylate.

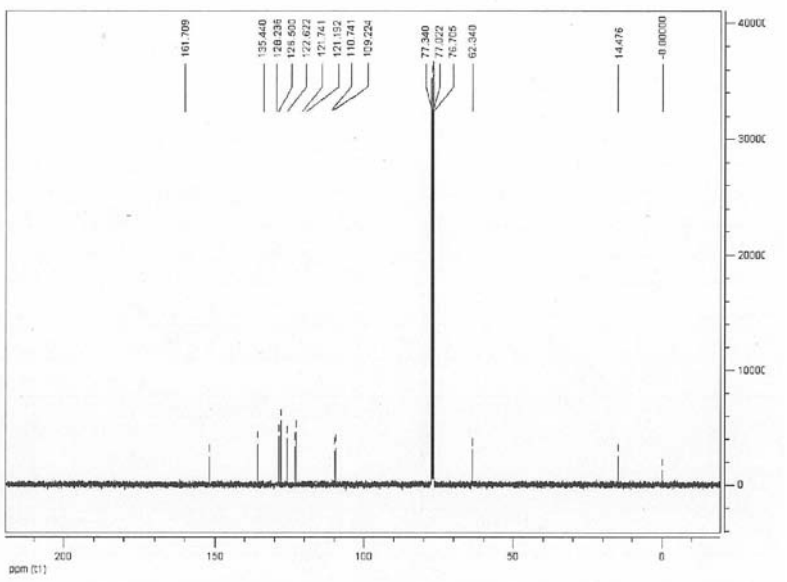

Figure S13. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 1*H*-indole-2-carboxylate.

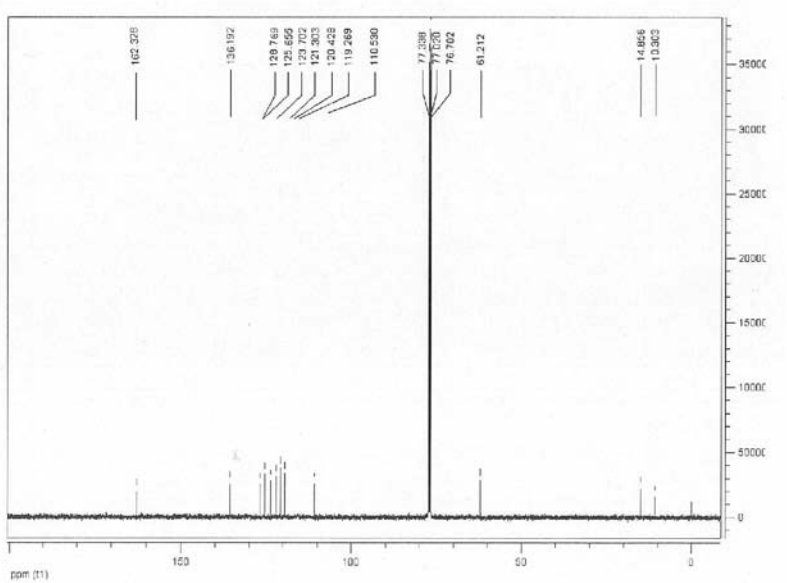

Figure S14. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 3-methyl-1*H*-indole-2-carboxylate.

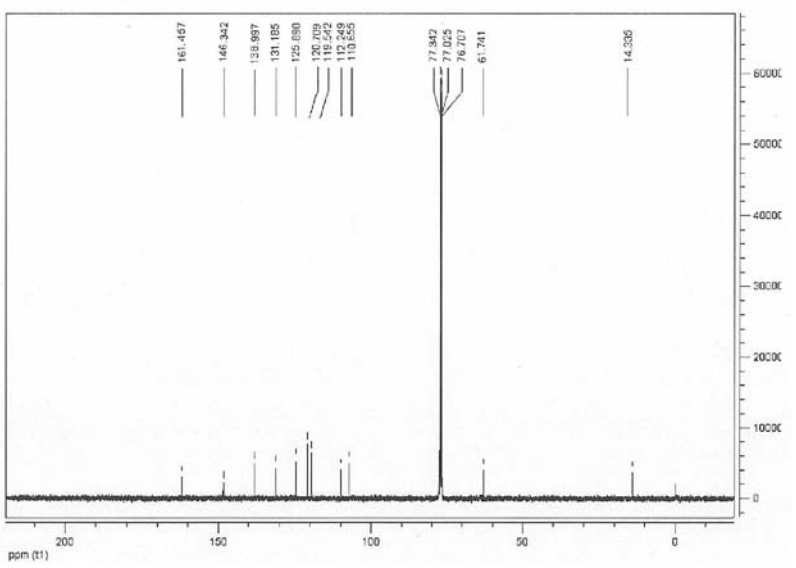

Figure S15. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 5-nitrol-1*H*-indole-2-carboxylate.

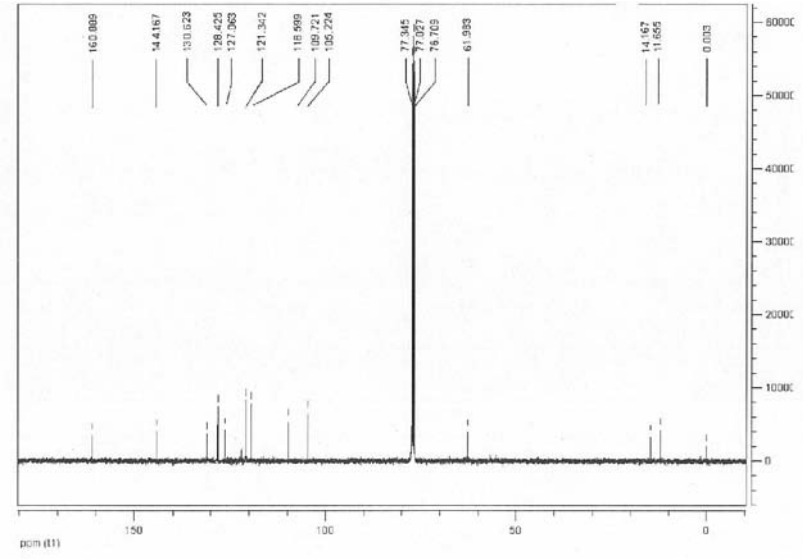

Figure S16. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 6-methoxyl-3-methyl-1*H*-indole-2-carboxylate.

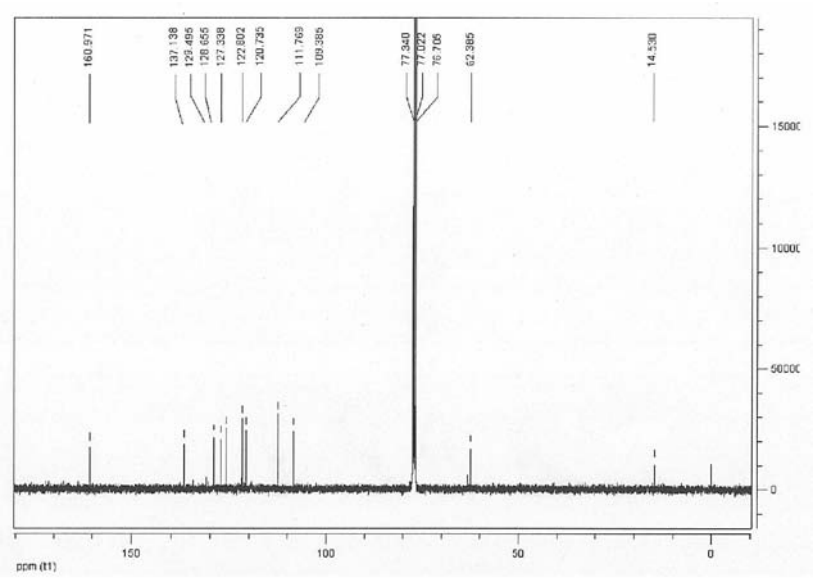

Figure S17. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 5-chloro-1*H*-indole-2-carboxylate.

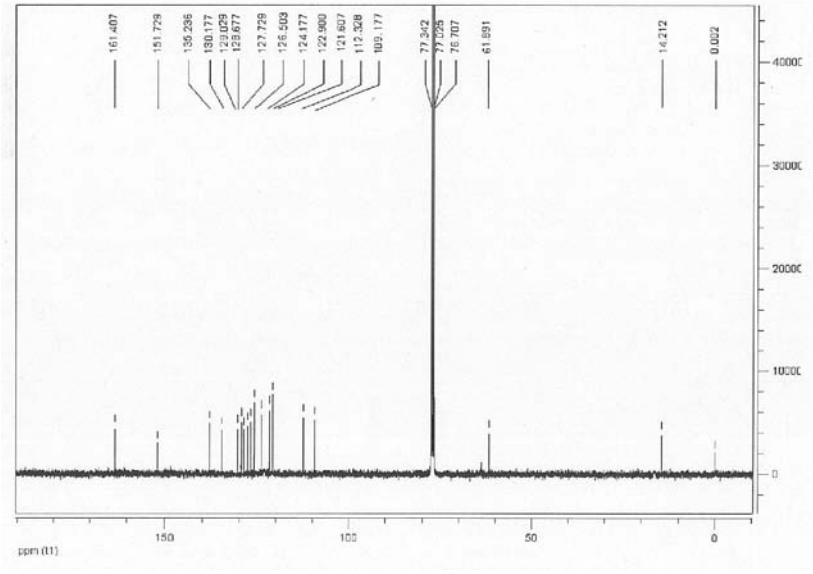

Figure S18. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 1*H*-benz[e]indole-2-carboxylate.

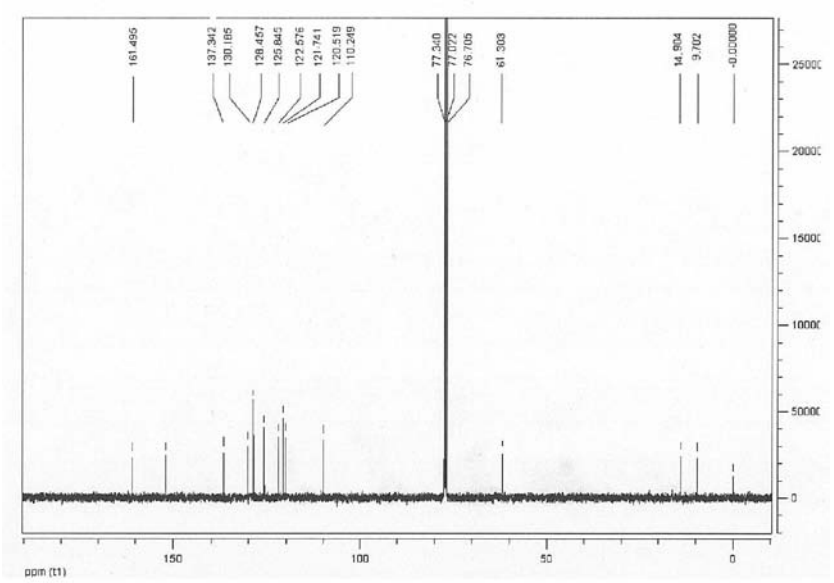

Figure S19. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 6 chloro-3-methyl-1*H*-indole-2-carboxylate.

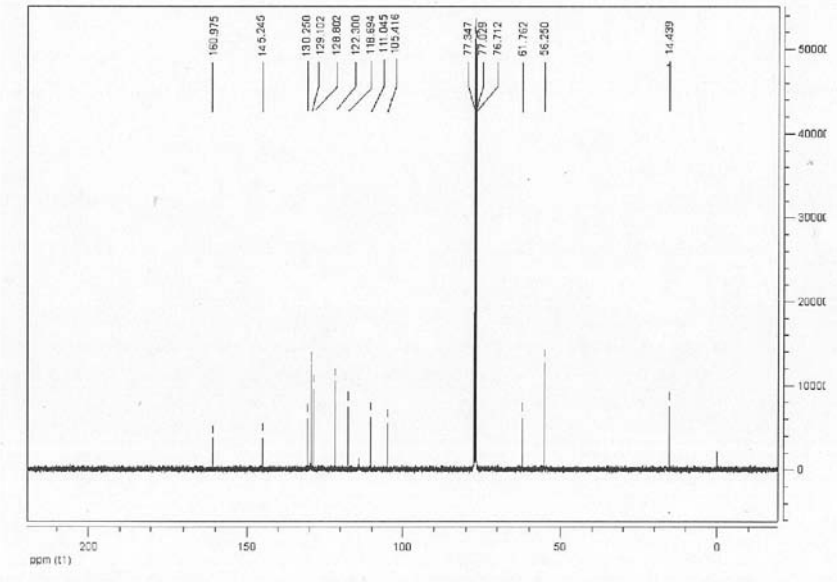

Figure S20. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 7-methoxyl-1*H*-indole-2-carboxylate.

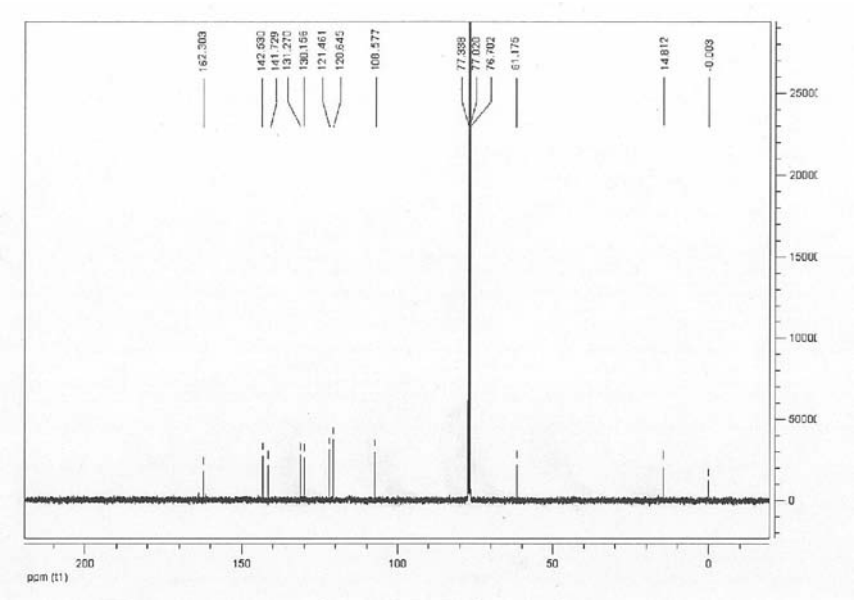

Figure S21. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 1*H*-pyrrolo[3,2-b]pyridine-2-carboxylate.

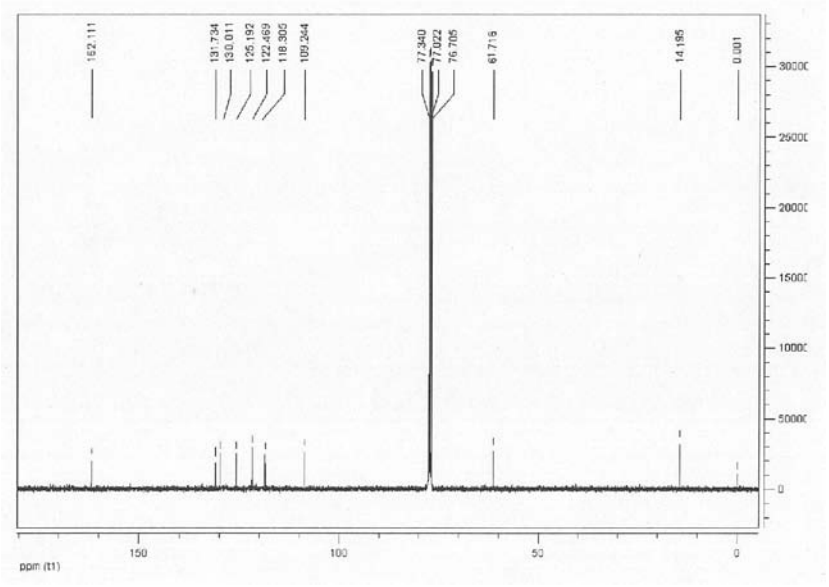

Figure S22. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl thieno[3,2-b]pyrrole-5-carboxylate.

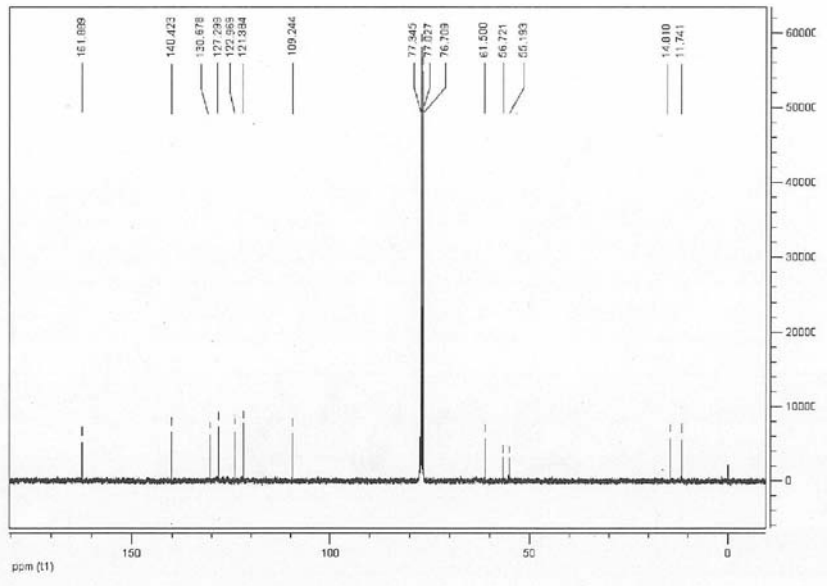

Figure S23. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 6-methyl-thieno[3,2-b]pyrrole-5-carboxylate.

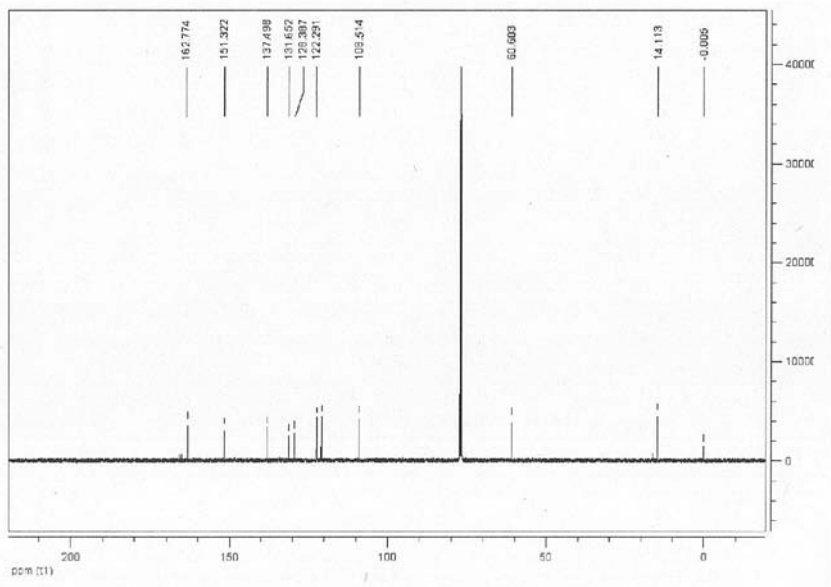

Figure S24. ^{13}C NMR spectrum ($CDCl_3$, 75 MHz) of ethyl 2-nitrothieno[3,2-b]pyrrole-5-carboxylate.