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Condensation Products of 3-Aminothiophenes with Acid Anhydrides

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Condensation of substituted 3-aminothiophenes with six different carboxylic acid anhydrides resulted in the formation of three types of products: N-(substituted thienyl) imides, substituted carboxylic acids and fused thieno[3,2-b]pyridines. The IR, NMR and MS spectra of these compounds are discussed.

Key Words: Condensation products, 3-Aminothiophenes, Acid anhydrides.

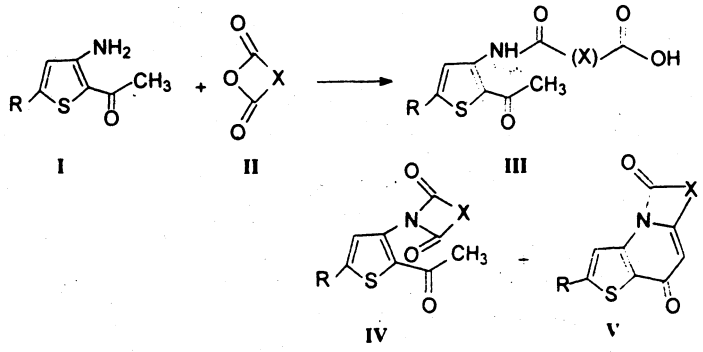
INTRODUCTION

Derivatives of 3-aminothiophene were used in different ways to prepare a variety of substituted thiophenes as well as fused thieno heterocyclic systems. We have previously reported the synthesis of a series of thieno[3,2-b]pyridines starting from 2-acetyl-3-aminothiophenes[1]. These fused thiophenes were also prepared from 3-aminothiophenes *via* α-vinylation followed by acid-catalysed cyclization using HBr/AcOH.[2] A thiophene ring bearing *o*-amino-β-ketoester moiety was cyclized with DMF-dimethylacetal and glacial acetic acid to give thieno[3,2-b]pyridines[3]. The benzothieno[3,2-b] pyridine ring system was obtained from the reaction of N-(3-benzo[b]thienyl) iminophosphorane with α,β-unsaturated ketones[4]. The related heterocyclic system dithieno[3,2-b:2′,3′-e]pyridines was prepared from the acid catalyzed reaction of 3-aminothiophene with one-half equivalent of aliphatic or aromatic aldehydes[5]. Other derivatives of these heterocyclic systems were also prepared and tested for biological activities[6,7]. On the other hand, 3-amino-2-carbamoylthiophene was prepared and treated with cycloalkanones to give 2-carbamoyl-3-cycloalkylidenaminothiophenes[8]. Condensation of 3-aminothiophene-2-carbonitrile with 2,5-dimethoxy tetrahydrofuran gave 1-[3-(thienyl-2-carbonitrile] pyrrole which was used further for the preparation of derivatives of pyrrole[1,2-a]thieno[2,3-f][1,4]diazepines[9].

In this paper, we are reporting results obtained when substituted-3-aminothiophenes are condensed with acid anhydrides.

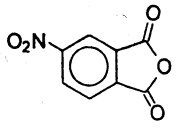
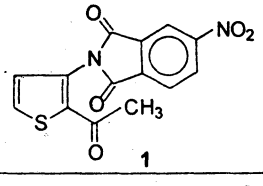
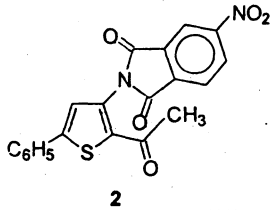
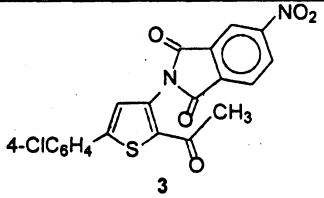
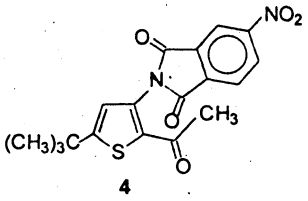
RESULTS AND DISCUSSION

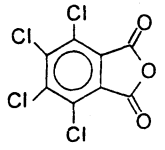
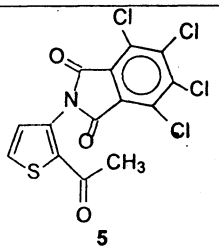
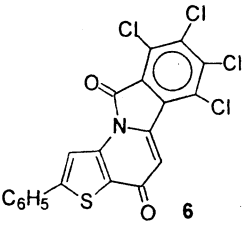
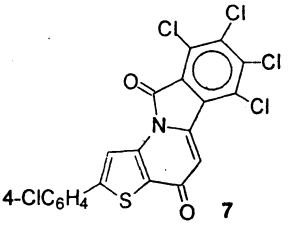
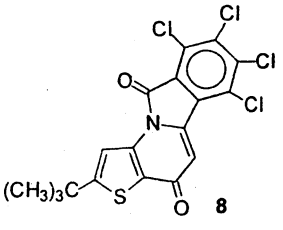
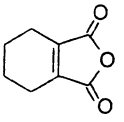
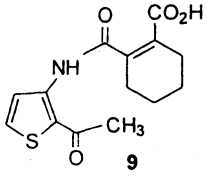
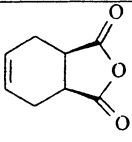
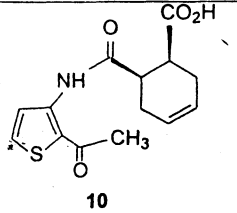
Reaction of 2,5-disubstituted-3-aminothiophenes with six different acid anhydrides gave three types of products, half-acid/half-amide **III**, imides **IV** and thieno [3,2-b] pyridines **V**. The acids used were derivatives of phthalic, tetrahydrophthalic and pyridinedicarboxylic anhydrides.

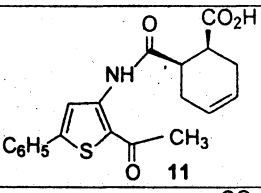
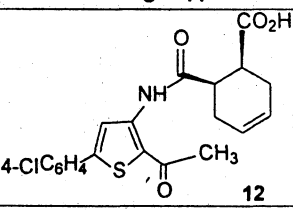
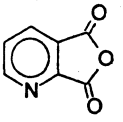
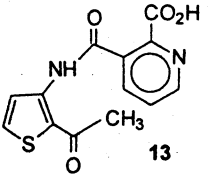
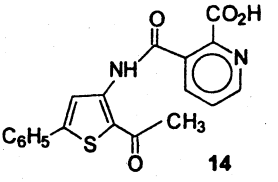
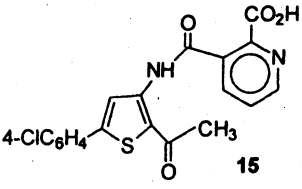
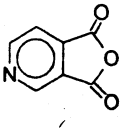
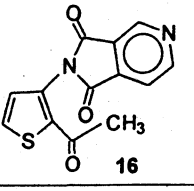


Scheme 1

TABLE-1
CONDENSATION PRODUCTS OF 2,5-DISUBTITUTED THIOPHENES WITH ACID ANHYDRIDES

Acid anhydride	R	Condensation Product
	H	 1
	C_6H_5	 2
	4-ClC_6H_4	 3
	$(CH_3)_3C$	 4

	H	 **5**
	C_6H_5	 **6**
	4-ClC_6H_4	 **7**
	$(CH_3)_3C$	 **8**
	H	 **9**
	H	 **10**

	C_6H_5	 11
	4-ClC_6H_4	 12
	H	 13
	C_6H_5	 14
	4-ClC_6H_4	 15
	H	 16

Sixteen different compounds of all three types were obtained. It was found that in general the type of product obtained is mostly dependent on the acid anhydride while the substituent on the thiophene ring has little effect.

4-Nitrophthalic anhydride

Condensation of **I** with 4-nitrophthalic anhydride gave products of type **IV**. Imides **1-4** were obtained as sole products. Their IR spectra displayed two carbonyl absorbances at 1726 cm^{-1} for the imide carbonyl group and 1670 cm^{-1} for the ketonic group. The ^1H NMR spectra of these imides showed a singlet in the range δ 2.46–2.52 for the acetyl methyl group. Protons of the imide moiety

appeared as follows: doublet at δ 8.10 with ortho coupling (J = 8–10 Hz) for H_6, the two ortho protons to the nitro group (H3, H5) absorbed near to each other so that they consist one multiplet at about δ 8.60–8.75. Although the expected pattern would be as a doublet (with meta coupling) for H_3 and doublet of doublet (with ortho and meta coupling) for H_5, it was so difficult to realize that in the actual spectra the two thiophene protons of **1** appeared as two doublets at δ 7.17 for H_4 and 7.63 for H_5 with J = 6.0 Hz, while the thiophene proton H_4 of compounds **2** and **3** absorbed in the same range with protons of the phenyl groups such that it could not be distinguished from them. In compound **4**, this position appeared as a singlet at δ 6.93.

The MS spectra of compounds **1–4** showed a general fragmentation pathway which consists of the molecular ion (M^+), M^+-15 (loss of CH_3), (M^+-15)-46 (loss of NO_2 from the latter fragment), [(M^+-15)-46]-28 (loss of CO from the latter fragment), and M^+-43 (loss of CH_3CO). Some common fragments are found in the spectra of all these compounds, such as m/z 63 $(C_5H_3)^+$, 75 $(C_6H_3)^+$, 103 $(C_6H_3CO)^+$, 119 $(C_6H_3OCO)^+$. It is probably worth mentioning here that in the MS spectrum of **3** an M + 2 peak is observed with about 35% from M^+ due to the presence of chlorine, and that in all four MS spectra of **1–4** no fragment peak coming from the loss of the substituent on the thiophene ring is observed except when that substituent is the t-butyl group (compound **4**) where a fragment peak at m/z 315 (loss of t-butyl) is present with high intensity.

Tetrachlorophthalic anhydride

Condensation of all four thiophene derivative with this acid anhydride gave the fused heterocyclic system thieno [2′,3′:5,6]pyrido[2,1-a]isoindole except when R=H which gave the imide **5**. The latter compound showed in its ^{1}H NMR spectrum a singlet for the methyl group at δ 2.51 and two doublets at δ 7.14 (H_4) and δ 7.68 (H_5) with J = 6.5 Hz for the thiophene protons. The MS spectrum of **5** displayed peaks for M^+ + 4, M^+ + 2 and M^+ at m/z 411, 409 and 407 respectively which are attributed to the presence of the four chlorine atoms. Its fragmentation pathway consists of loss of CH_3, CH_3CO thienyl-$COCH_3$ and consecutive loss of the four chlorine atoms.

Structures of the fused heterocyclic systems **6–8** were confirmed based upon the following spectroscopic observations. Their IR spectra displayed absorbance for the two carbonyl groups at about 1750 and 1620 cm^{-1} with the latter attributed to the ketonic carbonyl group. Their ^{1}H NMR spectra, on the other hand, confirmed their structures. The signal for the methyl group of **5** was no longer present in the spectra of **6–8**. A new signal appeared instead at about δ 7.30 for the C-10 proton. This is in agreement with our previous studies on such ring systems except that its position has shifted downfield due to the presence of the four chlorine substituents[1]. The C-3 proton of **6** and **7** appeared as a singlet at about δ 8.40 while that of **8** appeared at δ 8.0. The presence of the phenyl group at position 2 of **6** and **7** shifted the signal for position 3 downfield compared with the t-butyl group of **8**. The MS spectra of **6-8** showed their expected molecular ions in addition to the M^+ + 4 and M^+ + 2 peaks. Their fragmentation pathway is initiated by the loss of two CO molecules, loss of the substituent at position 2

is not observed except in **8** where the loss of the t-butyl group gives rise to a weak fragment at m/z 390 (6%).

Tetrahydrophthalic anhydride

Two derivatives of this acid anhydride were used, the first being 3,4,5, 6-tetrahydrophthalic anhydride while the other one is the *cis*-1,2,3,6-tetrahydrophthalic anhydride. In both cases condensation of these acids with thiophene (**I**) gave the half-acid half-amide products **9–12.** These compounds showed in their IR spectra broad absorbances in the range 3400–2600 cm^{-1} for the carboxylic acid group and three carbonyl absorbances at about 1700, 1680 and 1620 for the acid, ketone and amide groups, respectively. The ^1H NMR spectra of compounds **9–12** showed a low field signal for the carboxylic acid proton beside signals for the methyl and thiophene protons simiar to those in compounds **1–4**. The acid moiety protons of **9** appeared as two multiplets, four protons each at δ 1.81 and 2.50. In derivatives **10–12** these protons are split into three groups. The four protons at C_3 and C_6 appeared as a multiplet at δ 2.50, while the two protons at C_1 and C_2 appeared as another multiplet at δ 3.1. Protons of the double bond gave rise to one broad signal at δ 5.75 which is in agreement with previous studies on such compounds[10].

The MS spectra **9–12** showed weak to moderate molecular ions with weak fragment peaks rising from the loss of water and CH_3 group.

Pyridinedicarboxylic anhydride

Two derivatives of this acid anhydride were used. They were the 1,2- and 2,3-dicarboxylic anhydrides. Condensation of the former with **I** gave the half acid half amide products **13–15**, while the latter gave the imide **16**. Compounds **13–15** displayed in their IR spectra the usual broad absorbance for carboxylic acids in the range 3400–2400 cm^{-1} beside the carbonyl group absorbances at about 1700, 1684 and 1625 cm^{-1} for the acid, ketone and amide groups. Compound **16**, in contrast, did not show any absorbance related to a carboxylic acid group, but rather only two carbonyl group absorbances similar to its analogue, compound **1**. The ^1H NMR spectra of **13–15** showed similar pattern to their previous analogues **9–12**, except for the pyridine ring protons which appeared as two multiplets in the range 7.60–8.80 with 2 : 1 ratio. In compound **16** these protons appeared as one multiplet.

The MS spectra of **13–15** displayed a moderate molecular ion with an M+2 peak for **15** due to the presence of the chlorine substituent. Their fragmentation pathway is initiated *via* the loss of water and CH_3CO group. Compound **16,** on the other hand, showed a very strong molecular ion with the base peak being M^+—CH_3.

In conclusion, we have shown that condensation of 2-acetyl-3-aminothiophenes with four types of acid anhydrides gave imides, half acid, half-imide and the fused heterocyclic system thieno[2′,3′:5,6]pyrido[2,1-a]isoindole. The type of acid anjydride appeared to control which product is obtained.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer as KBr pellets and expressed as ν (cm^{-1}). NMR spectra were recorded on Jeol FX-100 (100 MHz) and Jeol ECP 400 (400 MHz) in $CDCl_3$ or DMSO and expressed as δ (ppm). MS spectra were recorded on Shimadzu QP-5050A GC/MS system.

General procedure for the condensation of 2-acetyl-3-aminothiophene with acid anhydrides

A solution of 3.5 mmole of **I**, 1.2 equivalents of acid anhydride, and 2 mL of trimethylamine in 50 mL xylene was refluxed at 150°C for 6 h. The solvent was evaporated under vacuum and the resulting oil was digested with ethyl ether to precipitate the products. Those products which were not pure on TLC were recrystallized from ethanol.

N-[2′-Acetyl-3′-thienyl]-4-nitrophthalimide, 1

Colourless powder, 52%, m.p. 153°C. IR (cm^{-1}): 1726, 1670, ν(CO), 1537, 1348 $\nu(NO_2)$. ^1H NMR: 2.52 (s, 3H), 7.17 (d, J = 6.0 Hz, 1H), 7.63 (d, J = 6.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H). 8.63–8.75 (m. 2H). MS: m/z 316 (M^+, 41), 301 (M^+—CH_3, 100), 273 (4), 255 (59), 227 (6), 199 (8), 171 (11), 152 (9), 127 (12), 119 (8), 103 (8), 75 (44), 63 (6).

N-[2′-Acetyl-5′-phenyl-3′-thienyl]-4-nitrophthalimide, 2

Colourless powder, 48% yield, m.p. 211°C. ^1H NMR: 252 (s, 3H), 7.42–7.66 (m, 6H), 8.13 (d, J = 10.0 Hz, 1H), 8.66–8.75 (m, 2H). MS: m/z 392 (M^+, 76), 377 (M^+—CH_3, 100), 347 (28), 331 (49), 246 (15), 172 (6), 121 (7), 119 (5), 103 (18), 75 (25), 63 (4).

N-[2′-Acetyl-5′-(4-chlorophenyl)-3′-thienyl]-4-nitrophthalimide, 3

Colourless powder, 61% yield, m.p. 184°C. ^1H NMR: 2.52 (s, 3H), 7.25–7.56 (m, 5H), 8.11 (d, J = 8.0 Hz, 1H), 8.64–8.77 (m, 2H). 'MS: m/z 428 (M^+ + 2, 17), 426 (M^+, 48), 413 (38), 411 (M^+—CH_3, 100) 383 (3), 365 (64), 337 (2), 281 (10), 264 (17), 201 (6), 155 (9), 119 (12), 103 (24), 75 (60) 63 (7).

N-[2′-Acetyl-5′-t-butyl-3′-thienyl]-4-nitrophthalimide, 4

Colourless powder, 41% yield, m.p. 191°C. ^1H NMR: 1.46 (s, 9H), 2.46 (s, 3H), 6.93 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.60–8.74 (m, 2H). MS: m/z 372 (M^+, 85), 357 (M^+—CH_3, 100), 329 (12), 315 (52), 311 (37), 283 (11) 269 (35), 251 (11), 240 (36), 196 (8), 149 (10), 119 (18), 103 (28), 75 (59), 63 (13).

N-[2′-Acetyl-3′-thienyl]-3,4,5,6-tetrachlorophthalimide, 5

Brownish powder, 45% yield, m.p. 253 °C. ^1H NMR: 2.51 (s, 3H), 7.14 (d, J = 6.5 Hz, 1H), 7.68 (d, J = 6.5 Hz, 1H). MS: m/z 411 (M^+, + 4, 14), 409 (M^+ + 2, 43), 407 (M^+, 32), 394 (409—CH_3, 100) 366 (3) 248 (2), 270 (5), 214 (15), 177 (8), 152 (52), 142 (15), 96 (8), 64 (7).

6,7,8,9-Tetrachloro-2-phenylthieno[2′,3′:5,6]pyrido[2,1-a]isoindole-5, 11-dione, 6

Light yellow needles, 57% yield, m.p. 300°C. IR (cm^{-1}) 1760, 1624 ν(CO). ^1H NMR: 729 (s, 1H), 7.53 (m, 3H), 7.82 (m, 2H), 8.41 (s, 1H). MS: m/z 469 (M^+ + 4, 50), 467 (M^+ + 2, 100), 465 (M^+, 75), 437 (M^+—CO, 34), 409 (437—CO, 2), 374 (409—Cl, 11), 339 (374—Cl, 4), 304 (339—Cl, 9), 269 (304—Cl, 3), 219 (26), 187 (11), 169 (16), 152 (8), 102 (8), 77 (9), 63 (5).

6,7,8,9-Tetrachloro-2(4′-chlorophenyl)thieno[2′,3′:5,6]pyrido[2,1-a]isoindole-5,11-dione, 7

Light yellow needles, 51% yield, m.p. 330°C. IR (cm^{-1}): 1753, 1620 ν(CO). ^1H NMR: 7.32 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 8.45 (s, 1H). MS: m/z 503 (M^+ + 4, 63), 501 (M^+ + 2, 100), 499 (M^+, 59), 473 (501—CO, 55), 471 (M^+—CO, 21), 410 (24), 338 (19), 302 (5), 267 (6), 236 (48), 205 (29), 187 (13), 155 (12), 64 (5).

2-tert-Butyl-6,7,8,9-tetrachlorothieno[2,3:5,6]pyrido[2,1-a]isoindole-5,11-dione, 8

Colourless powder, 39% yield, m.p. 320°C. IR (cm^{-1}): 1745, 1615 ν(CO). ^1H NMR: 1.48 (s, 9H), 7.44 (s, 1H), 8.00 (s, 1H). MS: m/z 449 (M^+ + 4, 15), 447 (M^+ + 2, 26), 445 (M^+, 14), 432 (447—CH_3, 100) 430 (M^+—CH_3, 61), 404 (432, —CO, 7), 390 (M^+-t-Bu, 6), 376 (404 —CO, 5), 203 (10), 188 (22), 156 (8), 132 (4), 93 (3), 69 (6), 64 (3).

2-[N-(2′-Acetyl-3′-thienyl)amido]-3,4,5,6-tetrahydrobenzoic acid, 9

Colourless powder, 43% yield, m.p. 149°C. ^1H NMR: 1.81 (m, 4H), 2.41 (s, 3H), 2.50 (m, 4H), 6.65 (d, J = 5.0 Hz, 1H), 7.30 (d, J = 5.0 Hz, 1H), 11.15 (bs, 1H). MS:m/z 293 (M^+, 4), 275 (M^+—H_2O, 2), 260 (275, —CH_3, 4), 232 (2), 206 (2), 152 (6), 141 (85), 126 (100), 108 (38), 79 (76, 71 (18).

Cis-2-[N-(2′-Acetyl-3′-thienyl)amido]-1,2,3,6-tetrahydrobenzoic acid, 10

Colourless powder, 35% yield, m.p. 147°C. IR (cm^{-1}): 3446–2600 ν(CO_2H), 1699 ν(CO, acid), 1681 ν(CO, ketone), 1625 ν(CO, amide). ^1H NMR: 2.50 (s, 3H), 2.62 (m, 4H), 3.18 (m, 2H), 5.75 (bs, 2H), 7.48 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 5.0 Hz. 1H), 11.38 (bs, 1H). MS: m/z (%) 293 (M^+, 9), 275 (M^+—H_2O, 4), 233 (4), 168 (6), 142 (100), 141 (73), 126 (93), 79 (69), 77 (29).

Cis-2-[N-(2′-Acetyl-5′-phenyl-3′-thienyl)amido]-1,2,3,6-tetrahydrobenzoic acid, 11

Colourless powder, 33% yield, m.p. 218°C. ^1H NMR: 2.40 (m, 4H), 2.50 (s, 3H), 3.05 (m, 2H), 5.75 (bs, 2H), 7.33–7.40 (m, 5H), 8.46 (s, 1H), 11.25 (bs, 1H). MS: m/z 369 (M^+, 46), 351 (M^+—H_2O, 17), 327 (29), 257 (23), 244 (18), 218 (100), 217 (73), 202 (81), 130 (17), 79 (38), 77 (26).

Cis-2-[N-(2′-Acetyl-5′-(4-chlorophenyl)-3′-thienyl)amido-1,2,3,6-tetrahydrobenzoic acid, 12

Colourless powder, 36% yield, m.p. 163°C. IR (cm^{-1}): 3447–2800 ν(CO_2H), 1713 ν(CO, acid), 1684 ν(CO, ketone), 1625 ν(CO, amide), ^1H NMR: 2.50 (s, 3H), 2.67 (m, 4H), 3.18 (m, 2H), 5.76 (bs, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 8.42 (s, 1H), 11.43 (bs, 1H). MS: m/z 403 (M^+, 8), 385

(M^+—H_2O, 5), 343 (8), 316 (43), 301 (100), 255 (63), 236(55), 199 (14), 171 (21), 124 (27), 79 (61).

3-[N-(2′-Acetyl-3′-thienyl)amido]pyridine-2-carboxylic acid, 13

Brownish powder, 43% yield, m.p. 215°C. IR (cm^{-1}): 3235–2400 ν(CO_2H), 1718 (CO, acid), 1684 ν(CO, ketone), 1623 ν(CO, amide). ^1H NMR: 2.56 (s, 3H), 7.40 (bs, 1H), 7.60 (m, 2H), 8.0 (d, J = 5.0 Hz, 1H), 8.31 (d, J = 5.0 Hz, 1H), 8.78 (m, 1H), 12.94 (bs, 1H). MS: m/z 290 (M^+, 31), 272 (M^+—H_2O, 2) 247 (M^+—CH_3CO, 100), 229 (18), 203 (64), 152 (11), 141 (37), 126 (91), 106 (32), 94 (25), 78 (35).

3-[N-(2′-Acetyl-5′-phenyl-3′-thienyl) amido]pyridine-2-carboxylic acid, 14

Colourless powder, 29% yield, m.p. 214°C. IR (cm^{-1}): 3406–2600 ν(CO_2H), 1708 ν(CO, acid), 1682 ν(CO, ketone), 1633 (CO, amide). ^1H NMR: 2.57 (s, 3H), 7.41 (m, 5H), 7.82 (m, 2H), 8.21 (m, 1H), 8.62 (s, 1H), 8.82 (bs, 1H), 12.95 (bs, 1H). MS: m/z 366 (M^+, 52), 348 (M^+—H_2O, 5), 323 (M^+—CH_3CO, 100), 305 (6), 279 (78), 244 (12), 217 (18), 202 (68), 147 (8), 122 (11), 94 (18), 78 (23).

3-[N-(2′-Acetyl-5′-(4-chlorophenyl-3′-thienyl)amido]pyridine-2-carboxylic acid, 15

Browish powder, 47% yield, m.p. 167°C. ^1H NMR: 2.46 (s, 3H), 7.49 (m, 2H), 7.77 (m, 2H), 8.07 (m, 1H), 8.44 (s, 1H), 8.78 (m, 1H), 9.06 (m, 1H), 11.92 (bs, 1H), 12.60 (bs, 1H). MS: m/z 402 (M^+ + 2, 9), 400 (M^+, 31), 357 (M^+—CH_3CO, 100), 339 (8), 313 (95), 278 (17), 251 (26), 236 (81), 181 (9), 150 (13), 122 (16), 106 (88), 94 (28), 78 (90).

N-(2′-Acetyl-3′-thienyl)pyridine-3-4-dicarboximide, 16

Colourless powder, 41% yield, m.p. 155°C. ^1H NMR: 2.51 (s, 3H), 7.15 (d, J = 5.0 Hz, 1H), 7.35 (m, 3H), 7.66 (d, J = 5.0 Hz, 1H). MS: m/z 272 (M^+, 95), 257(M^+—CH_3, 100), 229 (M^+—CH_3CO, 5), 201 (23), 173 (20), 152 (22), 141 (20), 126 (28), 105 (21), 86 (78), 78(13).

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