The conversions of isothiazolium salts into thiophenecarboxylic ester derivatives

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This paper is dedicated to Professor Gerald E. Dunn on the occasion of his 65th birthday

DAVID M. MCKINNON, K. ANN DUNCAN, and LESLEY M. MILLAR. Can. J. Chem. **62**, 1580 (1984).

Several 3-aminothiophene-2-carboxylic ester derivatives are made by reaction of potassium 3-ethoxy-3-oxopropanoate with isothiazolium salts or by reaction with 2-ethoxy-2-oxoethylidenedimethylsulfurane. In the latter case deaminated products are also isolated. These products are consistent with initial nucleophilic attack on the sulfur atom of the isothiazolium salt. In one case a pyrrole derivative is formed by a novel rearrangement of an intermediate aziridine derivative. Some further derivatives of 3-benzylaminobenzo[*b*]thiophene are described.

DAVID M. MCKINNON, K. ANN DUNCAN et LESLEY M. MILLAR. Can. J. Chem. **62**, 1580 (1984).

On a préparé plusieurs esters de l'acide amino-3 thiophène carboxylique-2 en faisant réagir l'éthoxy-3 oxo-3 propanoate de potassium avec des sels d'isothizaolium ou avec l'éthoxy-2 oxo-2 éthylidènediméthyl-sulfuranne. Dans ce dernier cas, on a également isolé des produits de désamination. Ces produits correspondent à une attaque nucléophile initiale sur l'atome de soufre du sel d'isothiazolium. Dans un cas, il se forme un dérivé du pyrrole selon une nouvelle transposition d'un dérivé aziridine intermédiaire. On décrit quelques autres dérivés de le benzylamino-3 benzo[*b*]thiophène.

[Traduit par le journal]

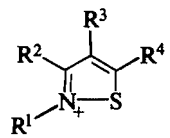
Introduction

Nucleophilic attack by some stable carbanions at the ring sulfur atom of both monocyclic isothiazolium salts **1** and 1,2-benzisothiazolium salts has been demonstrated (1, 2). The final isolated products are frequently thiophene or benzo[*b*]thiophene derivatives respectively, formed by recyclization of initial reaction products. For example, the reaction of phenacylidenedimethylsulfurane with 2,5-diphenylisothiazolium perchlorate (**1***a*) afforded 3-anilino-2-benzoyl-5-phenylthiophene. An alternative approach to this type of compound used sodium benzoylacetate, behaving as a potential phenacyl ion, reacting with 2,5-diphenyl-3-methylthioisothiazolium perchlorate (**1***b*). In this case the final aromatization is effected by loss of a group that was originally on the isothiazolium ring. In view of the potential of aminothiophenecarboxylic acids in the synthesis of fused thiophene heterocycles, analogous to the preparation of fused heterocycles from anthranilic acid derivatives, we have investigated their preparation by methods analogous to these.

Results and discussion

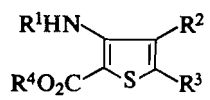
Since we have earlier demonstrated that in these reactions sodium benzoylacetate functions as a potential phenacyl ion, accordingly, in this work, we used potassium 3-ethoxy-3-oxopropanoate as a source of the anion of ethyl acetate. Thus, when it was treated with 2-benzyl-3-methylthio-1,2-benzisothiazolium perchlorate (**1***c*), ethyl 3-benzylaminobenzo[*b*]thiophene-2-carboxylate (**2***b*) was obtained in high yield. This reaction likely proceeds by initial attack of the anion on the ring sulfur atom, forming an acyclic intermediate which then recyclizes, forming the thiophene by loss of methanethiol (Scheme 1, X = SCH_3). Likewise 2-methyl-3-methylthio-1,2-benzisothiazolium perchlorate (**1***d*) gave ethyl 3-methylaminobenzo[*b*]thiophene-2-carboxylate (**2***c*).

Treatment of monocyclic isothiazolium salts **1***e*,*g* similarly successfully gave the thiophene-2-carboxylic ester **3***b* in moderate yield. In these cases the final aromatization is by loss of an amine function, as these compounds lack alkylthio leaving groups in suitable positions. For the compound **1***h*, the thiophene derivative **3***c* was obtained along with methyl 3-methylamino-2-phenyldithiopropenoate (**4**). Had attack of the nucleophile occurred at carbon-5 of the salt, methanethiol would likely have been eliminated to provide a reductant, as is known for some 2,1-benzisothiazolium cation reactions (3).



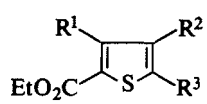
1

a R¹ = Ph; R² = R³ = H; R⁴ = Ph
b R¹ = Ph; R² = SMe; R³ = H; R⁴ = Ph
c R¹ = $PhCH_2$; R² = SMe; R³, R⁴ = —(CH=CH)₂—
d R¹ = Me; R² = SMe; R³, R⁴ = —(CH=CH)₂—
e R¹ = Ph; R² = H; R³ = Ph; R⁴ = H
f R¹ = Ph; R² = H; R³ = Ph; R⁴ = SMe
g R¹ = Me; R² = H; R³ = Ph; R⁴ = H
h R¹ = Me; R² = H; R³ = Ph; R⁴ = SMe
i R¹ = R² = Me; R³ = R⁴ = H



2

a R¹ = Me; R² = H; R³ = Ph; R⁴ = Et
b R¹ = $PhCH_2$; R², R³ = —(CH=CH)₂—; R⁴ = Et
c R¹ = Me; R², R³ = —(CH=CH)₂, R⁴ = Et
d R¹ = Ph; R² = Ph; R³ = H; R⁴ = Et
e R¹ = Ph, R² = Ph; R³ = SMe; R⁴ =Et
f R¹ = Me; R² = Ph, R³ = H; R⁴ = Et
g R¹ = Me; R² = Ph; R³ = SMe; R⁴ = Et
h R¹ = Ph; R² = Ph; R³ = SMe; R⁴ = Me



3

a R¹ = R² = H, R³ = Ph
b R¹ = H, R² = Ph; R³ = H
c R¹ = H, R² = Ph, R³ = SMe

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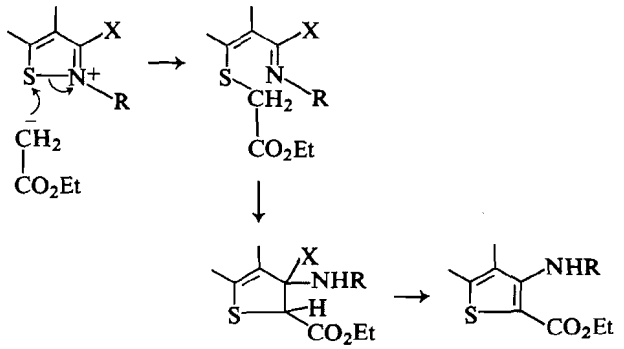


SCHEME 1

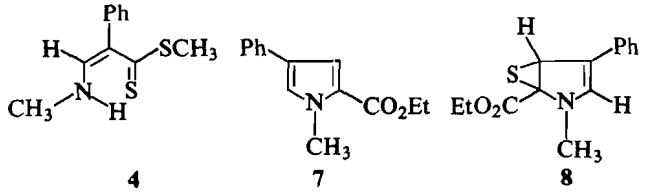
Indeed, treatment of the salt **1***h* with sodium methanethiolate did provide the aminodithioester **4** in good yield. However, we have not been able to isolate any reaction product arising from nucleophilic attack at carbon.

Another possible approach to the desired amino esters would be by using the anion of ethyl acetate stabilized as an ylid. Accodingly, 2-ethoxy-2-oxoethylidenedimethylsulfurane was treated with the five monocyclic isothiazolium salts **1***a*, *e*–*h*, and in each case we obtained the expected 3-aminothiophene-2-carboxylic ester derivatives **2***a*, *d*–*g*, i.e. products consistent with initial attack of the ylid at ring sulfur (Scheme 2). However, the intermediate **5** could form the ester **2** in several ways. One possible pathway is via an aziridine **6** (Scheme 2, path a) as suggested (4) by analogy with the known formation of aziridines from imines and sulfur ylids (5). Nevertheless, we consider that another pathway, involving a β-elimination, is more likely, especially for the formation of unsaturated esters of type **2** (Scheme 2, path b). This is discussed below.

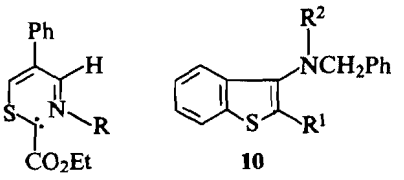
In three cases, **1***a*, *e*, and *f* the aminoesters **2** were accompanied by products which did not contain an amino function, i.e. **3***a*, *b*, and *c* respectively. Likewise **1***h* also gave **3***c* (the nitrogen atom and substituent are lost in the reaction). One possibility is that there is some reduction stage in the reaction, involving loss of the sulfonium moiety, so that eventual aromatization ocurs by loss of amine. This reduction may be by the ethanol solvent or by a nucleophilic displacement on the exocyclic sulfur atom. Various stabilized carbanions or equivalent are known to be displaceable from the corresponding sulfides (6–8). Another possibility is that there may be bond formation between the sulfur and nitrogen atoms, producing a four-membered ring or transition state analogous to the intermediates of Wittig reactions, with final elimination of an azasulfonium ylid (Scheme 2, path c). Although the occurrence of "σ-tetravalent" sulfur in the four-membered ring is not impossible (9), there do not appear to be any earlier literature reports of a reaction such as path c, and it may represent an unusual reaction product of sulfonium ylids.

When the isothiazolium salt **1***g* was treated with ylid, the pyrrole derivative **7** was obtained as a minor product. A possible source for its formation would be the episulfide **8**, since it is known that these readily extrude sulfur, especially when aromatic structures are produced (10). The episulfide itself could be formed from the aziridine **6** by a number of possible rearrangement mechanisms. Although we have shown one ionic mechanism (Scheme 3), there are in fact a number of methods, involving other ionic mechanisms or pericyclic reactions, whereby the conversion might be effected. The pyrrole **7** has not been previously synthesized. Its structure was proved by hydrolysis and decarboxylation to the known 1-methyl-3-phenylpyrrole. While isothiazolium salts have been used in the preparation of other heterocyclic systems, these reactions have usually involved retention of the sulfur atom. This reaction therefore is of a new type, where the nitrogen atom is retained instead, and it may have potential in the synthesis of pyrrole derivatives.

Another plausible mechanism for the formation of the aziridines **6** would be from a carbene **9**, produced by α-elimination from the sulfonium ylid, such as are known (11).



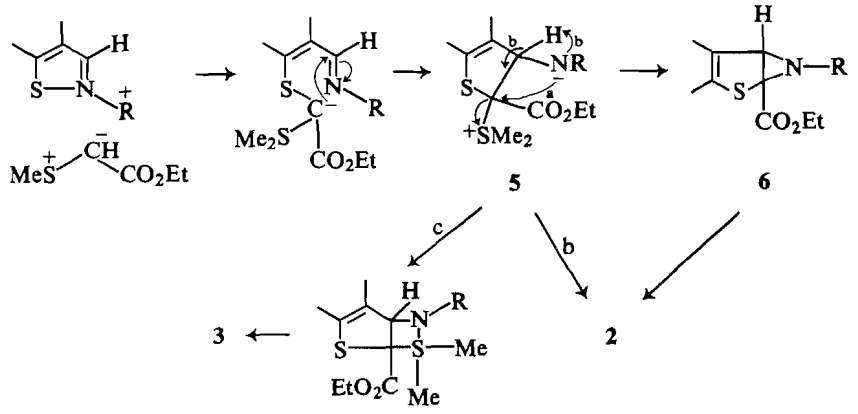
4 **7** **8**



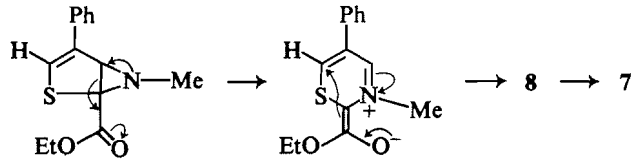
9 **10**

a R¹ = CO_2H; R^2 = H
b R¹ = H; R^2 = CO_2Et
c R¹ = CO_2Et; R^2 = CO_2Et
d R¹ = $CON(CH_2)_4$; R^2 = H

Whatever the actual mechanism for the formation of the pyrrole **7**, in each case an aziridine appears a probable inter-



SCHEME 2



SCHEME 3

mediate. Since there appears to be little reason why any such aziridine should not convert to the corresponding pyrrole, and yet pyrrole products were not obtained from the isothiazolium salts **1***a*, *e*, *f*, we favor the β-elimination pathway (Scheme 2, path b) for these. Possibly in these cases the nitrogen atom, bearing an aryl substituent, would be less nucleophilic and less able to displace dimethyl sulfide to form the aziridine. However, in one case, **1***h*, which is an *N*-methylisothiazolium salt, no pyrrole was obtained. Other factors may therefore be implicated.

The reaction of 2,3-dimethylisothiazolium perchlorate (**1***i*) with the ylid gave a number of products which we have been unable to identify.

We attempted to produce aminothiophenecarboxylic esters using a nitrogen ylid, the anion of *N*-(2-methoxy-2-oxoethyl)-pyridinium bromide, and treatment with the isothiazolium salt (**1***f*) gave methyl 3-anilino-5-methylthio-4-phenylthiophene-2-carboxylate (**2***h*). The yield of this, however, was lower than the ester formed using the sulfonium ylid.

Since N-substituted anthranilic acids serve as synthetic precursors of isatoic anhydrides and thence 2,1-benzisothiazoles (12, 13), we attempted comparable conversions of the amino-acid **10***a*, produced by basic hydrolysis of the ester **2***b*, in an attempt to prepare thieno[3,2-*c*]isothiazole derivative. The acid **10***a* only gave the urethane **10***b* on treatment with ethyl chloroformate. The acid contains structural elements resembling anthranilic acids and thiophene-2-carboxylic acids, both of which decarboxylate readily. Treatment of **2***b* directly gave the ester **10***c*, and thionation of the amide **10***d*, prepared from the ester **2***b* and pyrrolidine, gave a complex mixture from which no thioamides, possible precursors of isothiazoles, could be isolated.

Although the nitrogen atom in compound **10***d* would be expected to have sp^2 hybridization, due to its attachment both to a thiophene ring and a carbonyl group, the neighboring benzylic protons were evident as two doublets, indicating their non-equivalency. It thus appears that steric constraints force the nitrogen atom into an sp^3 hybridization, rendering the benzylic protons diastereotopic. Rapid inversion at nitrogen is also precluded by steric hindrance.

Experimental

The ^{1}H nmr spectra were obtained in deuteriochloroform solution using tetramethylsilane as an internal standard, on a Varian model E.M. 360 spectrometer. Mass spectra were obtained on a Finnigan model 1015 spectrometer, and thick-layer chromatography (tlc) was performed on "Camag" silica gel type D.S.F.5 supplied by Terochem laboratories. Where necessary, solutions were dried over anhydrous magnesium sulfate.

*Reactions of isothiazolium salts (**1**) with potassium 3-ethoxy-3-oxopropanoate*

To the isothiazolium salt (~1 mmol) in anhydrous ethanol (10 mL) was added potassium 2-ethoxy-2-oxopropanoate (1.5 mmol) and the mixture heated gently until complete reaction (~5 min). The solutions were diluted with water and extracted with chloroform. The dried evaporated extracts were thick oils which were purified by chromatography using benzene or chloroform as eluents, depending on the polarity of products. In some cases the products crystallized on standing. For the product **2***b* no chromatography was necessary and it was crystallized from ethanol. Results are summarized in Table 1.

*Reactions of isothiazolium salts (**1**) with 2-ethoxy-2-oxoethylidene-dimethylsulfurane*

2-Ethoxy-2-oxoethyldimethylsulfonium bromide (1.5 mmol) in ethanol (10 mL) was treated with sodium ethoxide (1.5 mmol) and to the solution was added the isothiazolium salt (1 mmol). The mixtures were warmed until homogeneous and the solutions were worked up as above. Results are summarized in Table 2. In general, although both thiophenecarboxylic esters (**3**) and aminothiophenecarboxylic esters (**2**) chromatographed at similar R_f values, satisfactory separation was obtained by varying the eluents.

*Reaction of 2,4-diphenyl-3-methylthioisothiazolium perchlorate with N-(2-methoxy-2-oxoethyl)pyridinium bromide to form **2**h*

To a solution of sodium (46 mg) dissolved in ethanol (10 mL) was added the pyridinium salt (232 mg, 1.0 mmol) and the mixture swirled until homogeneous. Then the isothiazolium salt (384 mg, 1.0 mmol) was added, and the mixture warmed until homogeneous. Work-up by the procedures used above for sulfonium ylids gave the ester as an oil which crystallized on standing. It was finally recrystallized from ethanol as pale yellow needles, mp 158°C (19%).

The nmr spectrum, δ: 2.47 (3H, s, S—CH_3), 3.71 (3H, s, CO_2Me), 6.5–7.4 (10H, m, aromatic), 8.45 (broad N—H). The mass spectrum: M^+ 355, M calcd. 355. *Anal.* calcd. for $C_{19}H_{17}NO_2S_2$: C 64.23, H 4.79, N 3.94, S 18.03; found: C 64.41, H 4.82, N 3.81, S 18.22.

*Reduction of 2-methyl-5-methylthio-4-phenylisothiazolium perchlorate (**1**h) by methanethiol to methyl 3-methylamino-2-phenyldithiopropenoate (**4**)*

The salt **1***h* (1.0 mmol) was added to a sodium methanethiolate solution (prepared by passing excess methanethiol into a solution of sodium ethoxide) and the mixture warmed until homogeneous, then diluted with water. The dried chloroform extract gave yellow needles on evaporation. Recrystallization from hexane gave **4** as long yellow needles (60%). The product was identical (mixture mp, R_f, to that isolated above). The nmr spectrum, δ: 2.5 (3H, s, S—CH_3), 3.1–3.2 (3H, d, N—CH_3), 6.8–7.1 (1H, s, vinyl), and 7.2–7.5 (5H, m, aromatic).

*3-Benzylaminobenzo[b]thiophene-2-carboxylic acid (**10**a)*

The ester **2***b* (1 g, 3.02 mmol) in ethanol (10 mL) was treated with 20% aqueous sodium hydroxide solution (5 mL) and refluxed 3 h. The solvent was evaporated and the residue in water (10 mL) was adjusted to pH 4 with concentrated hydrochloric acid. The amino acid precipitated as a pale yellow powder, mp 125–126°C (94%), which was collected and dried. This was sufficiently pure for further reactions without recrystallization. The mass spectrum: M^+ 283, M calcd.: 283. *Anal.* calcd. for $C_{10}H_{13}NO_2S$: C 67.84, H 4.59, N 4.95, S 11.31; found: C 67.66, H 4.81, N 4.63, S 11.52.

*Ethyl N-benzyl-N-(3-benzo[b]thienyl)carbamate (**10**b)*

The acid **10***a* (0.707 g, 2.5 mmol) in ethyl chloroformate (10 mL) was refluxed 3 h. Evaporation of the solution yielded a viscous oil which crystallized on standing under cyclohexane. The material was recrystallized from cyclohexane as colorless needles, mp 76–78°C (85%). The nmr spectrum, δ: 1.15 and 4.20 (—CH_2—CH_3), 4.90 2H, s, CH_2—Ph), 6.99 (1H, s, the thiophene), 7.15–7.95 (9H, m, aromatic). *Anal.* calcd. for $C_{18}H_{17}NO_2S$: C 69.45, H 5.47, N 4.50, S 10.29; found: C 69.28, H 5.20, N 4.69, S 10.51.

*Reactions of ethyl 3-benzylaminobenzo[b]thiophene-2-carboxylate (**2**b) with pyrrolidine to form N-pyrrolidinyl-3-benzylamino-benzo[b]thiophene-2-carboxamide (**10**c)*

The ester **2***b* (1 g, 3.2 mmol) in pyrrolidine (10 mL) was heated in a closed vessel at 130°C for 16 h. Evaporation of the solution gave a semicrystalline oil which was crystallized from methanol as colorless

TABLE 1. Reactions of isothiazolium salts with potassium 3-ethoxy-3-oxopropanoate

Salt	Product	Yield (%)	Melting point (°C)	Formula	Analysis: Calculated C	H	N	S	Found C	H	N	S
1*c*	**2***b*	74	97–99	$C_{18}H_{17}NO_2S$	69.45	5.47	4.50	10.29	69.63	5.31	4.62	10.41
1*d*	**2***c*	89	41–42	$C_{12}H_{13}NO_2S$	61.28	5.53	5.96	13.62	61.36	5.61	5.81	13.44
1*e*	**3***d*	88	*	$C_{13}H_{12}O_2S$	67.22	5.21	—	13.80	67.28	5.31	—	13.80
1*g*	**3***d*	47	*									
1*h*	**3***c*	38	75–77	$C_{14}H_{14}O_2S_2$	60.40	5.07	—	23.03	60.27	5.09	—	22.80
1*h*	**4**	14	130–132	$C_{11}H_{13}NS$	59.15	5.87	6.27	28.71	59.14	5.83	6.16	28.74

*This product could not be crystallized.

TABLE 2. Reactions of isothiazolium salts with 2-ethoxy-2-oxoethylidenedimethylsulfurane

Salt	Product	Yield (%)	Melting point (°C)	Formula	Analysis: Calculated C	H	N	S	Found C	H	N	S
1*a*	**2***a*	9	90–91	$C_{19}H_{17}NO_2S$	70.56	5.26	4.33	9.91	70.61	5.30	4.26	9.90
	3*a*	30	‡	$C_{13}H_{12}O_2S$	67.22	5.21	—	13.80	67.26	5.29	—	13.58
1*e*	**2***d*	42	73–74	$C_{19}H_{17}NO_2S$	70.56	5.26	4.33	9.91	70.51	5.34	4.24	9.92
	3*b**	25	‡									
1*f*	**2***e*	36	122–123	$C_{20}H_{19}NO_2S_2$	65.01	5.18	3.79	17.35	64.93	5.21	3.66	17.28
	3*c**	40										
1*g*	**2***f*	52†	‡									
	7	30	53	$C_{14}H_{15}NO_2$	73.34	6.59	6.11	—	73.27	6.58	5.95	—
1*h*	**2***g*	47	99–100	$C_{15}H_{17}NO_2S_2$	58.6	5.57	4.56	20.86	58.46	5.61	4.41	20.96
	3*c**	30										

*See Table 1.

†This compound appears to decompose on standing; however, ms and nmr properties were consistent with this structure. (The mass spectrum: M^+ 261, M calcd. 261; the nmr spectrum, δ: 1.2–1.5 and 4.2–4.5 (3H, t, and 2H, q resp; CH_2—CH_3), 2.5–2.6 (3H, broad, N—CH_3), 6.6–6.8 (1H, N—H), 7.1 (1H, s, thiophene), 7.2–7.7 (5H, m, aromatic). When shaken with D_2O the broad peak at 2.5–2.6 collapsed into sharp singlet and that at 6.6–6.8 disappeared.)

‡This product was an uncrystallizable oil.

needles, mp 150–152°C (72%). The nmr spectrum, δ: 1.6–2.0 and 3.5–3.8 (two 4H, m, the pyrrolidinyl), 4.70 (2H, d, —CH_2—Ph), 7.1–8.0 (10H, m, aromatic and amino). The mass spectrum: M^+ 336, M calcd. 336. *Anal.* calcd. for $C_{20}H_{20}N_2OS$: C 71.43, H 5.95, N 8.33, S 9.52; found: C 71.52, H 6.03, N 8.54, S 9.63.

Attempted thionation of **10***c* in benzene with phosphorus pentasulfide gave only a small amount of a complex yellow oil on work-up.

Prepration of ethyl N*-benzyl-*N*-(2-ethoxycarbonylbenzo[*b*]thienyl) carbamate (**10**d)*

The ester **2***b* (1 g, 3.2 mmol) in ethyl chloroformate (5 mL) was refluxed 24 h. Evaporation of the solution gave a viscous colorless oil which did not crystallize but was purified by tlc in chloroform. The nmr spectrum, δ: 0.83–1.40 and 3.90–4.41 (two —CH_2—CH_3, superimposed), 4.60–5.25 (2H, q, the diastereotopic benzylic —CH_2—Ph), and 7.23–7.95 (9H, m, aromatic). The mass spectrum: M^+ 383, M calcd. 383. *Anal.* calcd. for $C_{21}H_{21}NO_4S$: C 65.80, H 5.48, N 3.66, S 8.36; found: C 65.88, H 5.62, N 3.49, S 8.45.

Preparation of 1-methyl-3-phenylpyrrole

The pyrrole **7** (15 mg) was refluxed 2 h in solution of potassium hydroxide (0.1 g) in 50% aqueous ethanol (5 mL). Work-up gave 1-methyl-4-phenylpyrrole-2-carboxylic acid as a colorless crystalline powder, mp 165–170°C. This was not further purified or analyzed. Heating at 180°C for 2 h gave 1-methyl-3-phenylpyrrole as a colorless crystalline sublimate, mp 43–44°C (lit. (14) mp 43–44°C) (90%).

Acknowledgements

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