Improved Syntheses of [3,2-*b*]- and [2,3-*b*]-fused Selenolo- and Thienopyrroles, and of Furo[3,2-*b*]pyrrole

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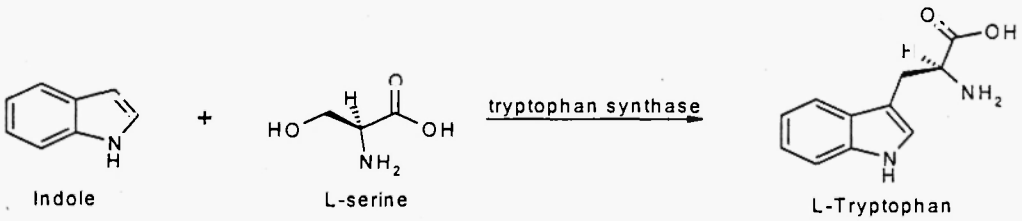
Abstract: 5-carboxyselenolo[3,2-*b*]pyrrole, 5-carboxyselenolo[2,3-*b*]pyrrole, 5-carboxythieno[3,2-*b*]pyrrole, and 5-carboxythieno[2,3-*b*]pyrrole are smoothly decarboxylated in glycerol at 160-170°C, providing greater than 70% yields of the corresponding pyrroles. Furo[3,2-*b*]pyrrole decarboxylates rapidly in refluxing ethanolamine to give greater than 50% yields of furo[3,2-*b*]pyrrole. By using these decarboxylation conditions, the previously described route to unsubstituted [3,2-*b*]- and [2,3-*b*]-fused selenolo- and thienopyrroles, and to furo[3,2-*b*]pyrrole, has been improved.

Introduction

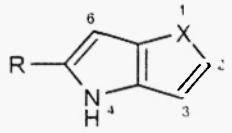
Tryptophan synthase catalyzes the reaction between indole and L-serine to create L-tryptophan (Scheme 1) (1). This enzyme has been used by our group (2-4), and others (5), in chemoenzymatic



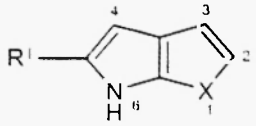
Scheme 1 The tryptophan synthase-mediated production of L-tryptophan

syntheses of several analogs of L-tryptophan, in which indole analogs were used in place of indole. In this way, we have recently synthesized 6-(4H-selenolo[3,2-*b*]pyrrolyl)-L-alanine and 4-(6H-selenolo[2,3-*b*]pyrrolyl)-L-alanine by substituting indole with selenolo[3,2-*b*]pyrrole and selenolo[2,3-*b*]pyrrole (Figure 1), respectively (6). It is our hope that these amino acids will be useful as heavy atom derivatives of L-tryptophan in protein x-ray crystallography, just as selena-L-methionine has been used in place of L-methionine (7).

Syntheses of selenolo[3,2-*b*]pyrrole and selenolo[2,3-*b*]pyrrole were reported in 1978 (8), though most of the synthetic strategy employed was derived from previous work (9). When repeating these syntheses, we made minor changes to certain reaction conditions and workup strategies, as evidenced in the Experimental section. However, we could not reproduce the published yields for the decarboxylations that form selenolo[3,2-*b*]pyrrole (35%) and selenolo[2,3-*b*]pyrrole (38%) from 5-carboxyselenolo[3,2-*b*]pyrrole and 5-carboxyselenolo[2,3-*b*]pyrrole, respectively. Instead, we found decarboxylation yields to be less than 5%.



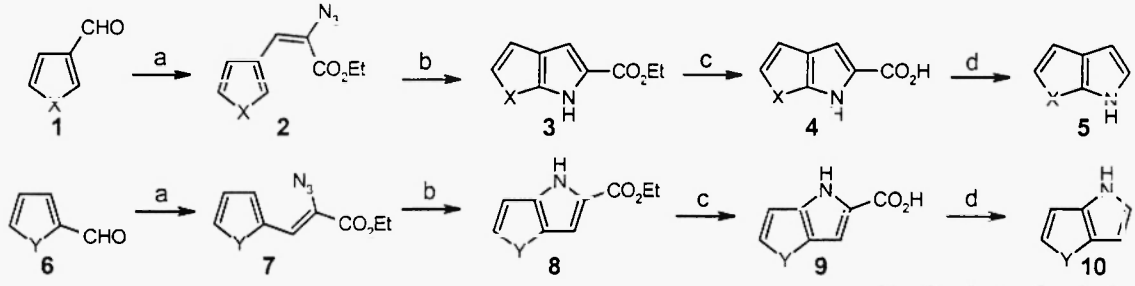
R	X	compound
H	Se	selenolo[3,2-*b*]pyrrole
H	S	thieno[3,2-*b*]pyrrole
H	O	furo[3,2-*b*]pyrrole
CO_2H	Se	5-carboxyselenolo[3,2-*b*]pyrrole
CO_2H	S	5-carboxythieno[3,2-*b*]pyrrole
CO_2H	O	5-carboxyfuro[3,2-*b*]pyrrole



R^1	X	compound
H	Se	selenolo[2,3-*b*]pyrrole
H	S	thieno[2,3-*b*]pyrrole
CO_2H	Se	5-carboxyselenolo[2,3-*b*]pyrrole
CO_2H	S	5-carboxythieno[2,3-*b*]pyrrole

Figure 1: Heteroaryl-fused pyrroles

The published synthesis (8) of either isomer of 5-carboxyselenolopyrrole (Scheme 2, **4**, X = Se; **9**, Y = Se) begins with the production of either selenophene-3-carboxaldehyde (**6**, X = Se) or selenophene-2-carboxaldehyde (**1**, Y = Se) from selenophene (not shown). However, the related sulfur- and oxygen-containing isosteres of 5-carboxyselenolopyrroles (**4**, X = S; **9**, Y = S,O) can be synthesized in an



X = Se, S; Y = Se, S, O

a.) $N_3CH_2CO_2Et$, NaOEt, EtOH, O°C, 2h; b.) xylenes, reflux 10 min.; c.) KOH, H_2O, reflux, 2h; d.) copper catalyst, quinoline, Δ

Scheme 2: Synthesis of [3,2-*b*]- and [2,3-*b*]-heteroaryl-fused pyrroles (Soth, et al)

analogous fashion, but starting from commercially available aldehydes of thiophene and furan (**1**, X = S; **6**, Y = S,O) (8). For this reason, and due to the high cost of selenophene, we decided next to study decarboxylations of these carboxylic acids. Thus, 5-carboxythieno[3,2-*b*]pyrrole (**9**, Y = S) , 5-carboxythieno[2,3-*b*]pyrrole (**4**, X = S), and 5-carboxyfuro[3,2-*b*]pyrrole (**9**, Y = O) were synthesized.

We first tried to cause the decarboxylation of these acids in hot quinoline, under copper catalysis, by following the published procedures of Soth, et al (8,10). Accordingly, copper powder was used in attempts to decarboxylate both 5-carboxythienopyrroles, while barium-promoted copper chromite was used for 5-carboxyfuro[3,2-*b*]pyrrole (this catalyst was also used for the 5-carboxyselenolopyrroles). Unfortunately, doing so gave very low yields (< 2%) of the desired thieno- and furopyrroles.

Of the aforementioned selenolo-, thieno-, and furopyrrole carboxylic acids, only 5-carboxythieno[3,2-*b*]pyrrole has been decarboxylated in another way. Snyder reported that it will decarboxylate "neat" – that is, without the presence of other materials or solvent – by heating it in a high vacuum (.02 mm Hg) (11). However, the yield of thieno[3,2-b]pyrrole so produced is low (36%) because of significant charring, and the sublimate contains unchanged 5-carboxythieno[3,2-*b*]pyrrole (12).

Because the published methods for causing the decarboxylation of these compounds were not, in our estimation, satisfactory, we were left to experiment with untried techniques. Thus, to our delight, we discovered that heating either isomer of 5-carboxythienopyrrole to 160-170 °C in glycerol resulted, after workup, in good yields of the desired pyrroles. The reaction mixtures gradually darkened over time, showing that the pyrroles were slowly destroyed as they formed. The reactions were quenched when gas evolution ceased. Starting from one gram of the corresponding acid, a 75% yield of thieno[3,2-*b*]pyrrole was obtained; reaction of a similar scale afforded a 73% yield of thieno[2,3-*b*]pyrrole.

Surprisingly, 5-carboxyfuro[3,2-*b*]pyrrole failed to transform into furo[3,2-*b*]pyrrole upon heating it in glycerol. Instead, the reaction mixture became slightly pink at 60 °C, when the acid was almost fully dissolved in glycerol. While heating to 130 °C, the solution gradually turned dark purple and became so viscous as to stop the magnetic stir bar. Gas formation was at no time evident, and workup revealed none of the targeted pyrrole. Instead, an intractable purple-brown solid resulted, which generated a difficult emulsion during attempted liquid-liquid extraction.

Fortunately, ethanolamine proved to be a good solvent for the decarboxylation of 5-carboxyfuro[3,2-*b*]pyrrole. Unlike glycerol, ethanolamine is able to deprotonate 5-carboxyfuro[3,2-*b*]pyrrole, thus allowing it to partially dissolve at room temperature. The transition from room temperature to 170 °C – the boiling point of ethanolamine – saw no evidence of color change or gas evolution. However, the lack of gas evolution is not surprising, as ethanolamine is used industrially as an absorbent of carbon dioxide. Alternatively, TLC was used to monitor the reaction, which proceeds rapidly at reflux. Starting with 0.66 g of 5-carboxyfuro[3,2-*b*]pyrrole, we obtained 50 – 70% yields of furo[3,2-*b*]pyrrole.

Having succeeded in the decarboxylations of our model compounds, we next tried to decarboxylate 5-carboxyselenolo[3,2-*b*]pyrrole and 5-carboxyselenolo[2,3-*b*]pyrrole in glycerol and ethanolamine. Either of these compounds decarboxylated efficiently in glycerol. Decarboxylation took place at the same temperature (160-170 °C) as with the 5-carboxythienopyrroles, and the reaction mixtures darkened as well. Yields were 70-75%. However, the 5-carboxyselenolopyrroles are quickly destroyed in refluxing ethanolamine. The solutions turned red, which we believe is due to deposition of colloidal selenium. Workup revealed none of the desired selenolopyrroles. However, when reaction temperatures were kept in the range 120-140 °C, optimized yields of 20-40% of selenolopyrroles were achieved over short reaction times (under ten minutes for hundreds of milligrams of carboxylic acid).

Discussion

In general, copper compounds have been used to catalyze decarboxylations of deactivated aromatic acids (13). However, their use is unnecessary for decarboxylations of selenolo-, thieno-, and furopyrrole carboxylic acids, which are highly activated.

We were inspired to use solvents in our decarboxylations by a description of how doing so can lessen the rate of thermal destruction to pyrroles which are formed at high temperatures (14). Our decision to use glycerol and ethanolamine owes to a description of them as "the solvents of choice" for decarboxylations of pyrrole-2-carboxylic acids (14).

Each of these pyrroles is very unstable. Exposure of TLC "spots" of these compounds to 0.1 M HCl turns them from invisible to black within minutes. When NMR samples of these pyrroles were prepared

using $CDCl_3$ as solvent, the solutions turned pink immediately. We attribute this to the presence of HCl in $CDCl_3$, because small amounts of these pyrroles cause 0.1 M solutions of HCl to turn pink as well. Left exposed overnight on a benchtop, they degrade to black tars. Storage at 0 °C allows [2,3-*b*]- and [3,2-*b*]-fused thieno- and selenolopyrroles to last for weeks. However, furo[3,2-*b*]pyrrole will turn black within four days regardless. All of these pyrroles immediately develop a purple-blue color upon exposure to Ehrlich's reagent (*p*-dimethylaminobenzaldehyde in 10% HCl) – a sign of their electron-rich character.

Conclusions

The synthetic route to [2,3-*b*]- and [3,2-*b*]-fused selenolo- and thienopyrroles, and to furo[3,2-*b*]pyrrole, originally described by Soth and co-workers, has been improved by changing the reaction conditions involved in the final decarboxylation step. Furo[3,2-*b*]pyrrole is decarboxylated in ethanolamine; the selenolo- and thienopyrroles in glycerol. The selenolo-, furo-, and thienopyrroles are unstable at room temperature and they quickly degrade in 0.1 M HCl. Furo[3,2-*b*]pyrrole is appreciably less stable than the [3,2-*b*]- and [2,3-*b*]-fused selenolo- and thienopyrroles.

Experimental

Starting Materials

Selenophene-2-carboxaldehyde (14) and selenophene-3-carboxaldehyde were prepared from selenophene, purchased from Aldrich (15,16). Thiophene-3-carboxaldehyde and thiophene-2-carboxaldehyde were purchased from Acros Organics. Furan-2-carboxaldehyde (furfural) was purchased from Aldrich. Ethyl azidoacetate was prepared from ethyl bromoacetate and sodium azide, as described below.

NOTE: numbers below in bold type refer to the compounds with those numbers in Scheme 2.

Ethyl azidoacetate

72.30 g (0.4329 moles) of 97% ethyl bromoacetate (CAUTION: strong lachrymator – work in fume hood) was dissolved in 200 mL of N,N-dimethylformamide and cooled to 0 °C. 28.14 g (0.4329 moles) of sodium azide was added slowly to the solution over 10 minutes. The reaction was allowed to warm to room temperature, and then left for 4 hours. Water was added to dissolve the sodium bromide by-product and the reaction mixture was transferred to a separatory funnel. Ethyl azidoacetate was extracted into ether. The ether extracts were combined and washed thrice with water, then once with brine, and dried over $MgSO_4$. Removal of ether *in vacuo* gave 47.17 g of ethyl azidoacetate (87%).

Ethyl 2-azido-3-(3'-selenienyl) acrylate (**2**, X = Se) (8)

This compound was synthesized as described by Soth and co-workers (8), starting from 7.00 g (0.0440 moles) selenophene-3-carboxaldehyde. However, it was chromatographically separated with a 9/1 hexanes/ethyl acetate solution as eluent rather than a 1/2 benzene/hexanes solution. Ethyl 2-azido-3-(3'-selenienyl) acrylate eluted before other products of the reaction, coming off the column as a pale yellow band. It was freed of solvent *in vacuo* and used without further purification. Yield was 7.13 g (60%), as noted by Soth, et al.

5-Carboethoxyselenolo[2,3-b]pyrrole (3, X = Se) (8)

1.18 g of ethyl 2-azido-3-(3'-selenienyl) acrylate (.00437 moles) was dissolved in 75 mL of xylenes and brought to reflux. After 10 minutes, the solution was cooled and the xylenes removed *in vacuo*. The

remaining solid was dissolved in the minimum amount of hot 2,2,4-trimethylpentane, immediately filtered, and the trimethylpentane was distilled off *in vacuo*. This yielded 0.90 g (85%) of 5-carboethoxyselenolo[2,3-*b*]pyrrole, which was found to be pure upon inspection of its ^{1}H NMR spectrum (8).

5-carboxyselenolo[2,3-b]pyrrole (4, X = Se) (8)

0.90 g of 5-carboethoxyselenolo[2,3-*b*]pyrrole (.0037 moles) was added to a solution of 0.56 g potassium hydroxide in 50 mL water, and heating begun. As the reaction proceeded, 5-carboethoxyselenolo[2,3-*b*]pyrrole, which was insoluble in the media, dissolved as the potassium salt. As soon as 5-carboethoxyselenolo[2,3-*b*]pyrrole was no longer evident, the reaction was allowed to cool, and transferred to a separatory funnel. The solutions was twice extracted with 10 mL portions of ether (which were discarded), then acidified with ice-cooled 5N HCl. This precipitated 5-carboxyselenolo[2,3-*b*]pyrrole, which was subsequently extracted with ether. The ethereal solution was washed twice with water, then once with brine, and dried over Na_2SO_4. Removal of ether yielded 0.79 g (100%) of 5-carboxyselenolo[2,3-*b*]pyrrole.

Selenolo[2,3-b]pyrrole (**5**, X = Se) (8)

0.79 g of 5-carboxyselenolo[2,3-*b*]pyrrole (.0037 moles) was added to 240 mL of glycerol and heating begun. The reaction was brought to 160-170 °C and maintained until carbon dioxide evolution was no longer evident (about 45 minutes), when it was quenched by pouring the solution over enough ice to cool it to room temperature. The solution was decanted free of excess ice into a separatory funnel. It was extracted thrice with ether. The extracts were pooled, washed twice with water, once with brine, and dried over Na_2SO_4. Removal of the ether afforded a mixture of white selenolo[2,3-*b*]pyrrole and an unidentified brown syrup. The selenolo[2,3-*b*]pyrrole was extracted away from the syrup with hot hexanes. Removal of hexanes provided 0.47 g (75%) selenolo[2,3-*b*]pyrrole, which proved difficult to recrystallize as described by Soth et al (8), and was thus stored at 0 °C without further purification. ^{1}H NMR ($DMSOd_6$+3 drops D_2O; 250 MHz, ppm): 7.38(d, 1H, *J* = 5.6 Hz), 7.15(d, 1H, *J* = 5.6 Hz), 7.04(d, 1H, *J* = 3.0 Hz), 6.38(d, 1H, *J* = 2.9 Hz).

Ethyl 2-azido-3-(2'-selenienyl) acrylate (**7**, Y = Se) (8), *ethyl 2-azido-3-(2'-thienyl) acrylate* (**7**, Y = S) (9), *ethyl 2-azido-3-(3'-thienyl) acrylate* (**2**, X = S) (9), *and ethyl 2-azido-3-(2'-furyl) acrylate* (**7**, Y = O) (9)

These compounds were synthesized in analogy with the procedure, described above, that was used to prepare ethyl 2-azido-3-(3'-selenienyl) acrylate. The starting aldehydes used were selenophene-2-carboxaldehyde, thiophene-2-carboxaldehyde, thiophene-3-carboxaldehyde, and furan-2-carboxaldehyde, respectively. All reactions were run on a similar scale to that described above for the synthesis of ethyl 2-azido-3-(3'-selenienyl) acrylate. The yields, contained in references 8 and 9, were 55%, 48%, 65%, and 46%, respectively.

5-Carboethoxyselenolo[3,2-b]pyrrole (**8**, Y = Se) (8), *5-carboethoxythieno[2,3-b]pyrrole* (**3**, X = S) (9), *5-carboethoxythieno[3,2-b]pyrrole* (**8**, Y = S) (9), *and 5-carboethoxyfuro[3,2-b]pyrrole* (**8**, Y = O) (9)

These were prepared starting with 1 – 2 g of the appropriate acrylates according to the procedure for synthesizing 5-carboethoxyselenolo[2,3-*b*]pyrrole. Yield, in all cases, was 85%.

5-Carboxyselenolo[3,2-b]pyrrole (**9**, Y = Se) (8), *5-carboxythieno[2,3-b]pyrrole* (4, X = S) (8), *5-carboxythieno[3,2-b]pyrrole* (**9**, Y = S) (8), *and 5-carboxyfuro[3,2-b]pyrrole* (**9**, Y = O) (8)

These were prepared from the appropriate ethyl esters on a similar scale and according to the procedure described for the synthesis of 5-carboxyselenolo[2,3-*b*]pyrrole. Yields were quantitative.

Selenolo[3.2-b]pyrrole (**10**, Y = Se) (8), *thieno[2,3-b]pyrrole* (**5**, X = S) (8). *and thieno[3,2-b]pyrrole* (**10**, Y = S) (8)

These were synthesized on a scale similar to and in analogy with the procedure described for selenolo[2,3-*b*]pyrrole. Their identities were confirmed by ^{1}H NMR inspection (8). Yields: selenolo[3,2-*b*]pyrrole (70%); thieno[3,2-*b*]pyrrole (75%); thieno[2,3-*b*]pyrrole (73%).

Furo[3,2-b]pyrrole (**10**, Y = O) (8)

0.09 g 5-carboxyfuro[3,2-*b*]pyrrole (.00060 moles) was dissolved in 25mL ethanolamine and brought to reflux, at which time reaction monitoring via reversed-phase TLC was begun. Towards this end, small volumes were periodically withdrawn via pipette from the reaction solution and doubled in volume by dilution with water. Ether extracts of these analytical fractions were eluted with water on reversed-phase TLC plates containing fluorescent indicator. The product pyrrole and the starting acid were both visible in the ultraviolet, and by staining with Ehrlich's reagent: R_f, 5-carboxyfuro[3,2-*b*]pyrrole = 0.89; R_f, furo[3,2-*b*]pyrrole = 0.16. When 5-carboxyfuro[3,2-*b*]pyrrole was no longer evident (within half an hour), the reaction was quenched by pouring it over enough ice to cool it to room temperature. The product was extracted into ether, washed with water and brine, then freed of solvent to reveal 0.04 g (67%) furo[3,2-*b*]pyrrole, which was stored at -70°C or used immediately. ^{1}H NMR (DMSO d_6; 250 MHz, ppm): 10.65(broad s, 1H), 7.49(d, 1H, J = 1.8 Hz), 6.85(d, 1H, J = 3.0 Hz), 6.56(d, 1H, J = 2 Hz), 6.11(d, 1H, J = 3.0 Hz)*.

*Each of these doublets should appear as doublets of doublets at high resolution (8).

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