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A one-step radical synthesis of pyrrol-2-acetic acids

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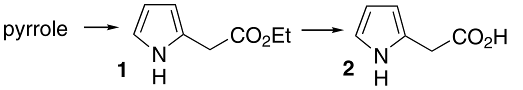
Abstract—Pyrrol-2-acetic acids were generated following a procedure involving I-transfer radical addition of iodoacetic acids to pyrrole with spontaneous loss of HI. This procedure also allows for efficient syntheses of 2-alkyl pyrroles through subsequent thermolytic decarboxylation.

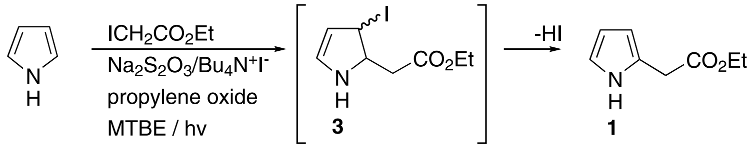
Pyrrol-2-acetic acids constitute an important class of compounds due to their use in a wide variety of molecules of pharmaceutical interest, most notably non-steroidal anti-inflammatory drugs such as tolmetin[1] and ketorolac.[2] There currently exist several modestly successful routes to esters of pyrrol-2-acetic acid (**1**), shown in Eq. (1). Friedel–Crafts acylation of pyrrole with ethoxalyl chloride,[3] followed by reduction of the resulting glyoxalate ester[4] led to generation of ester **1**, which could be alternatively generated upon treatment of pyrrole with ethyl diazoacetate in the presence of Cu(acac)$_2$.[5] More recently, radical methods have been used to synthesize these pyrrole acetate esters. Baciocchi[6] has utilized oxidative radical aromatic substitution methods (BEt$_3$, DMSO) to generate **1** in 47% yield.



(1)

We have previously reported atom-transfer radical addition methodology leading to formation of ester **1** in 90% yield.[7] In this methodology, C–C bond formation is proposed to occur in the course of I-transfer radical addition, as shown in Eq. (2). The putative addition product **3** spontaneously undergoes elimination of HI to generate substitution product **1**. Curran[8] has shown that a substoichiometric quantity of Bu$_3$SnSnBu$_3$ is required in I-transfer radical addition reactions in order to consume I$_2$, a radical chain suppressant which is generated as a byproduct of these reactions. In the course of our work,[7] we found that the addition of Na$_2$S$_2$O$_3$ as an I$_2$ reductant in the presence of the phase-transfer catalyst Bu$_4$N$^+$I$^-$ to aid in thiosulfate solubility provided an effective alternative to the use of distannanes. We also found that propylene oxide served as an effective HI trap.

Hydrolysis of ester **1** with aqueous NaOH has been reported to generate pyrrol-2 acetic acid (**2**, Eq. (1)) in 56% yield upon reacidification.[4] We were initially interested in seeing if our I-transfer radical aromatic substitution conditions would be amenable to the direct synthesis of **2**, negating the need for this low-yielding hydrolysis. Under our conditions, photolysis of iodoacetic acid in the presence of 15 equiv. of pyrrole led to formation of **2** in 72% yield (Eq. (3)). As in our previous work, the significant excess of pyrrole was necessary in order to minimize the formation of dialkylated products. Regioselectivities in this and all other radical reactions reported herein were outstanding, with barely detectable (by GC/MS) and non-isolable quantities of other isomeric products being formed.



(2)

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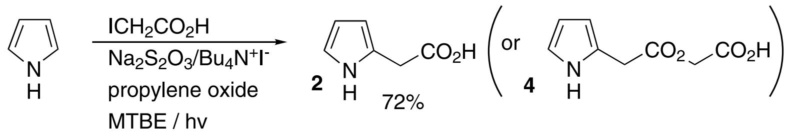
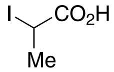
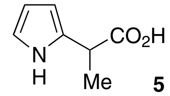
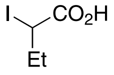
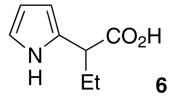
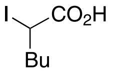
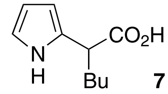
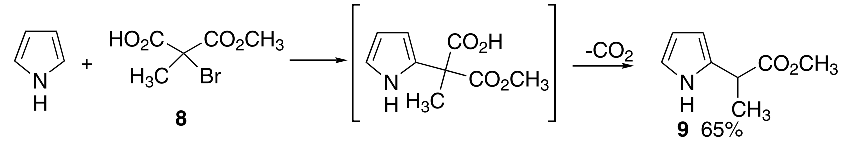


(3)

Table 1.

Iodide	Product	Yield
	 **5**	75%
	 **6**	90%
	 **7**	85%

The successful generation of **2** was dependent on careful control of the reaction temperature in the course of the photolysis. If the reaction temperature was allowed to warm above approximately 30°C, the major product obtained was acid **4**, presumably arising from nucleophilic attack of one of several possible carboxylic acid intermediates on iodoacetic acid, in addition to the desired radical substitution.



(4)

More highly substituted pyrrol-2-acetic acids have previously only been synthesized through the generation of the trianion of **2** with excess *t*-BuLi, followed by monoalkylation with an alkyl halide.[9] Thus, we were interested in seeing if our methodology would allow for direct generation of these alkylated acids. The modest variety of α-iodoacids in Table 1, generated upon treatment of commercially available α-bromoacids with NaI and catalytic $Bu_4N^+I^-$ in acetone, were successfully added to pyrrole under these conditions, leading to the products shown. Iodophenylacetic acid, on the other hand, failed to yield any substitution product, presumably due to the diminished reactivity of the benzylic radical. A typical procedure for the reaction is as follows: Pyrrole (2.02 g, 30 mmol), $Na_2S_2O_3$ (0.32 g, 2 mmol), propylene oxide (0.58 g, 10 mmol), $Bu_4N^+I^-$ (0.0074 g, 0.02 mmol) and 2.0 mmol of the desired iodoacid were dissolved in 4 ml of methyl *tert*-butyl ether (MTBE, distilled from CaH_2) in a screw-cap Pyrex test tube. The solution was cooled in an ice bath and deoxygenated with bubbling Ar for 10 min. Photolysis with an efficiently-cooled 450-W Hanovia lamp for 36 h resulted in complete consumption of the limiting iodoacid. Pyrrol-2-acetic acids could be isolated through flash chromatography on silica gel or extraction with aqueous base. The yields listed are for isolated and fully characterized products.[10]

It is also important to note that the known facile thermal decarboxylation of pyrrole-2-acetic acids[9,11] allows this methodology to serve as a highly regioselective synthesis of 2-alkyl pyrroles. This decarboxylation does, however, lead to the necessity of limiting the exposure of the acids to all but the mildest heat. Attempted GC/MS analysis of these acids also resulted in only the detection of the decarboxylated products, with the decarboxylation occurring due to the high temperature (250°C) in the injection port.

Attempted addition of malonate monoester **8** led to formation of ester **9** in 65% yield, presumably through a sequence of events involving radical substitution followed by decarboxylation, as shown in Eq. (4). Not surprisingly, the carboxylic acid functionality present in the intermediate is further labilized by the additional ester functionality. Acid **8** was generated by treatment of dimethyl methylmalonate with 1 equiv. of KOH in methanol. Purification of the saponification product was simplified by recrystallization of the sodium salt from MeOH with hot filtration prior to reacidification. Conversion of the monoacid to **8** was carried out by treatment with Br_2 in CH_2Cl_2.

In conclusion, we have demonstrated a convenient one-step synthesis of pyrrol-2-acetic acids, which also serves as an efficient entry into 2-alkyl pyrroles through subsequent thermal decarboxylation.

Acknowledgements

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10. Selected characterization data: Spectral data obtained for **5** and **9** are in close agreement with published data.[9] **2**: Prior to our work, only mp and combustion analysis data had been reported.[4] Mp 79–82°C (lit.[4] 82–84°C); ^{1}H NMR δ 8.9 (bs, 1H), 8.6 (bs, 1H), 6.80 (m, 1H), 6.25 (m, 1H), 6.10 (m, 1H), 3.72 (s, 2H); ^{13}C NMR δ 177.2, 122.7, 118.5, 108.9, 108.3, 33.5. **6**: ^{1}H NMR δ 11.02 (bs, 1H), 8.60 (bs, 1H), 6.79 (m, 1H), 6.21 (m, 1H), 6.14 (m, 1H), 3.65 (t, $J=7.0$ Hz, 1H), 1.92 (dq, $J=7.0$, 7.4 Hz, 2H), 1.02 (t, $J=7.4$ Hz, 3H); ^{13}C NMR δ 180.2, 127.7, 118.2, 108.7, 107.5, 46.7, 26.7, 12.4. Anal. calcd for $C_7H_{11}NO_2$: C, 62.74; H, 7.24; N, 9.15. Found: C, 62.48; H, 7.24; N, 8.86%. **7**: ^{1}H δ 10.20 (bs, 1H), 8.65 (s, 1H), 6.76 (m, 1H), 6.17 (m, 1H), 6.10 (m, 1H), 3.70 (t, $J=7.6$ Hz, 1H), 1.86 (dt, $J=7.6$, 7.0 Hz, 2H), 1.36 (m, 2H), 1.31 (m, 2H), 0.93 (t, $J=6.8$ Hz, 3H); ^{13}C δ 179.5, 127.9, 118.2, 108.7, 107.4, 44.9, 33.2, 29.9, 22.7. 14.2. Anal. calcd for $C_{10}H_{15}NO_2$: C, 66.27%; H, 8.34%; N, 7.73%. Found: C, 66.36%; H, 8.28%; N, 7.71%.
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