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Tandem radical-electrophilic annulations to pyrrole

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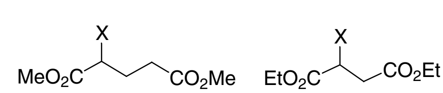
Abstract—Annulations to pyrrole arising from atom-transfer radical substitution, followed by electrophilic cyclization have been developed. These annulations provide for novel entries into the azabicyclo-[3.3.0] and azabicyclo-[3.4.0] ring systems.

In several previous publications we described novel synthetic methodology whereby radical aromatic substitution could be accomplished by a process involving iodine-transfer radical addition to heteroaromatics, accompanied by spontaneous rearomatization through loss of HI.[1] This methodology appears to be particularly useful for the synthesis of 2-substituted pyrroles with high regioselectivity. We had envisioned that radical methodology of this type might serve as the basis for annulations to pyrrole, creating bicyclic structures. More specifically, we had hoped to generate bicyclic structures through a tandem process involving intermolecular radical aromatic substitution, followed by ring closure arising from the nucleophilicity of the pyrrole nitrogen reacting with a pendant electrophilic functionality. We were particularly interested in reactions leading to the formation of azabicyclo-[3.3.0] and azabicyclo-[3.4.0] ring systems given their ubiquity in pyrrolizidine and indolizidine alkaloids, respectively. Previous radical-based attempts to synthesize these ring systems from pyrrole have started with an N-substituted pyrrole, with subsequent radical cyclization. Processes of this type involving the cyclization of nucleophilic alkyl or acyl radicals onto a pyrrole derivatized with an electron-withdrawing group are well precedented.[2] Similar cyclizations involving electrophilic radicals have also been observed,[3] as demonstrated in Muchowski's synthesis of the anti-inflammatory drug Ketorolac.[3b]

With the aforementioned goals in mind, we set out to synthesize iodoglutarate and iodomalate diesters. Based on previous results in our laboratory,[1] as well as others',[4] we knew that the ester functionality adjacent to the halogenated carbon should render the formed radical suitably electrophilic for addition to the electron-rich heteroarene, pyrrole, while the second ester should supply an electrophilic carbon for subsequent ring closure. Following literature procedures,[5] conversion of the commercially available monomethyl glutarate to its acid chloride with $SOCl_2$, followed by a Hell–Vollhard–Zelinsky reaction with Br_2, and esterification with refluxing CH_3OH yielded bromoester **1a**, shown in Figure 1. Conversion to α-iodoester **1b** was readily accomplished upon treatment of **1a** with NaI/acetone and catalytic $Bu_4N^+I^-$. The synthesis of homologous bromide **2a** has been previously accomplished by treatment of diethyl D,L-malate with CBr_4 and PPh_3.[6] We subsequently found that the same conversion can be carried out more conveniently and reproducibly using PBr_3 as the brominating agent in THF. Bromide **2a** was converted to iodide **2b** with a procedure identical to that used to synthesize **1b**.

With the above α-haloesters in hand, we attempted their addition to pyrrole following our previously established photolytic conditions. Curran et al.[7] has shown that a substoichiometric quantity of $Bu_3SnSnBu_3$ is required in I-transfer radical addition reactions in order to



1a X = Br
1b X = I

2a X = Br
2b X = I

Figure 1.

Keywords: Pyrrole; Radical; Pyrrolizidine; Indolizidine.
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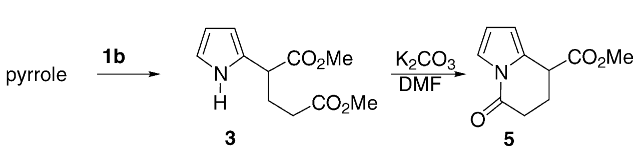
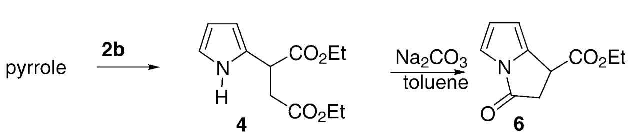
consume I_2, a radical chain suppressant, which is generated as a byproduct of these reactions. In the course of our previous work,[1] we found that the addition of $Na_2S_2O_3$ as an I_2 reductant in the presence of the phase-transfer catalyst $Bu_4N^+I^-$ to aid in thiosulfate solubility provided an effective alternative to the use of distannanes. We also found that propylene oxide served as an effective HI trap. The need to use a 15-fold excess of pyrrole in order to obtain synthetically useful yields of monosubstitution products is a drawback to this procedure, however.[1,4]

Bromoester **1a** underwent the desired radical reaction quite sluggishly, and in poor yield. While bromomalonates have been shown to undergo atom-transfer additions to pyrrole quite readily,[1] bromo precursors to monocarbonyl-stabilized radicals are apparently not sufficiently reactive to undergo reactions of this type in synthetically useful yields. This was probably due to the diminished rate with which atom transfer occurs with alkyl bromides relative to the more reactive iodides. The rate of halogen transfer to alkyl radicals by ethyl iodoacetate has been reported to occur about 10^3 faster than ethyl bromoacetate.[8] Radical aromatic substitution from iodoester **1b** proceeded smoothly, but isolation of the product was complicated by the presence of 1-iodo-2-propanol, the byproduct of HI trapping with propylene oxide.[1] The 1-iodo-2-propanol proved very difficult to remove from the crude product mixture, as it seemed to have nearly identical chromatographic mobility and a comparable boiling point to the desired pyrrole product **3**. This difficulty was effectively solved by substituting the less polar epoxide epoxydecane for propylene oxide. The iodoalcohol generated upon the reaction of epoxydecane with HI proved far less polar than the desired pyrrole, facilitating the chromatographic isolation of pyrrole **3** in 78% yield[9] (Eq. 1). The process also proceeded smoothly for the reaction of **2b** with pyrrole, generating **4** in 69% yield[9] (Eq. 2). The modest diminution in yield was probably due to HI elimination from the limiting reagent **2b**, resulting in small quantities of diethyl maleate and fumarate, identified in the crude reaction mixture by GC/MS.



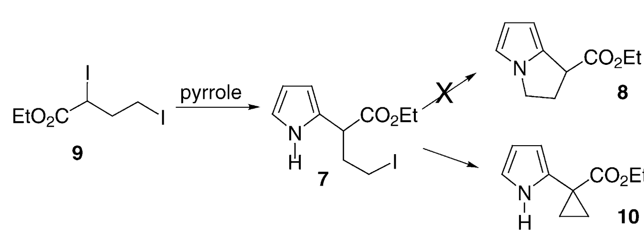
(1)



(2)

Cyclization of diester **3** was accomplished upon treatment with K_2CO_3 in refluxing DMF, generating a 60% yield of the desired bicyclic pyrrole **5**[10] (Eq. 1). Cyclization of diester **4** proved far more difficult than expected. At first, none of a large variety of reasonable cyclization strategies, involving a wide variety of bases and solvents, seemed to generate any of the desired lactam **6**. In order to shed some light on this problem, we calculated the reaction enthalpies for both the successful cyclization of **3**–**5**, as well as the heretofore unsuccessful cyclization of **4**–**6**. Calculations were carried out at the AM1 semi-empirical level using Spartan software, and predicted a ΔH_{rxn} of +4.4 kcal/mol for formation of **6**, and a ΔH_{rxn} of +0.1 kcal/mol for formation of **5**. While the precision of values obtained at this low level of theory are clearly suspect, they do support the conclusion that both cyclizations are nearly thermoneutral, with the formation of lactam **6** slightly more endothermic, probably due to enhanced ring strain. With this information in mind, we reasoned that if we distilled off the EtOH byproduct as it was generated, we might obtain lactam **6**. After attempting a variety of milder methods including removal of EtOH by azeotropic distillation, we found that we were only able to generate **6** in 43% yield upon treatment of **4** with K_2CO_3 in toluene, followed by distillation of the reaction mixture to dryness[11] (Eq. 2). Once formed, however, lactam **6** proved reasonably robust, and required no special handling.

Given the difficulties in cyclization of **4**, we envisioned that the azabicyclo-[3.3.0] ring system might be more easily obtained by cyclization of **7** to form **8**, owing to presumed diminished ring strain in **8** relative to **6**. Addition of ethyl 2,4-diiodobutyrate (**9**),[12] generated from the analogous dibromide[13] proceeded smoothly under our usual conditions for radical aromatic substitution to form **7** in 74% yield. Somewhat remarkably, the primary iodide functionality proved quite unreactive to the reaction conditions. Attempted cyclization under a wide variety of basic and neutral conditions failed to generate isolable quantities of **8**, instead generating cyclopropane **10**, presumably arising from the ester enolate. Treatment of iodide **7** with NEt_3 in refluxing EtOH proved optimal for the synthesis of cyclopropane **10** in 81% yield.[14] Problematic cyclopropane formation has also been observed with structurally similar 2-acylpyrroles.[15]



(3)

In conclusion, we have shown that our previously established methodology for radical aromatic substitution to pyrrole is effective with a wider variety of highly functionalized alkyl iodides. The substitution products, once formed, are capable of undergoing intramolecular lact-amization to form novel examples of the bicylic compounds bearing the azabicyclo-[3.3.0] and azabicyclo-[3.4.0] ring systems. We believe these examples to be the first case in which annulations to pyrrole have been performed via radical substitution followed by intramolecular electrophilic attack. The bicyclic pyrrole derivatives are also of interest, given that they illustrate novel derivatives of pyrroleacetic acids, a class of compounds noted for their anti-inflammatory and analgesic activity.[3b,16]

Acknowledgements

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9. General procedure for photolytic substitution reactions: A 1.00-mmol portion of alkyl iodide was combined with 1.01 g (15.0 mmol) of pyrrole, 0.313 g (2.00 mmol) of epoxydecane, 0.16 g (1.00 mmol) of $Na_2S_2O_3$ (freshly powdered with a mortar and pestle) and 0.036 g (0.100 mmol) of tetra-butylammonium iodide were dissolved in 4 mL of methyl *tert*-butyl ether in a 10-mL screw-cap Pyrex test tube. The mixture was deoxygenated with bubbling Ar, and photolyzed for 48 h with a 450-W medium-pressure Hanovia lamp. Solvents were removed by rotary evaporator, and the resulting crude oil was purified by medium pressure liquid chromatography (MPLC) with 15% ethyl-acetate/85% hexane (v/v) to yield the product.
   Dimethyl 2-(1*H*-pyrrol-2-yl)pentanedioate (**3**): Iodide **1b** was used to give 176 mg (78%) of **3** as an oil, homogeneous by TLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 6.75 (m, 1H), 6.13 (dd, J = 0.8 Hz, 1.6 Hz, 1H), 6.04 (m, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.30 (m, 2H), 2.15 (m, 2H), 1.30 (t, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 173.6 171.2, 127.4, 118.3, 108.7, 107.5, 52.5, 52.0, 43.9, 31.8, 28.7; IR (neat) 3385, 1730; GC/MS *m/z* 225. Anal. Calcd for $C_{11}H_{14}NO_4$: C, 58.70; H, 6.71; N, 6.22. Found: C, 58.60; H, 6.80; N, 6.20.
   Diethyl 2-(1*H*-pyrrol-2-yl)butanedioate (**4**): Iodide **2b** was used to give 162 mg (69%) of **4** as an oil, homogeneous by TLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 6.75 (m, 1H), 6.15 (dd, J = 2.9 Hz, 5.8 Hz, 1H), 6.04 (m, 1H), 4.19 (m, 5h), 3.11 (dd, J = 9.0 Hz, 16.7 Hz, 1H), 2.85 (dd, J = 5.6 Hz, 16.9 Hz, 1H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 172.7, 172.1, 127.4, 118.4, 108.7, 106.6, 61.8, 61.3, 40.9, 37.0, 14.5, 14.5; IR (neat) 3386, 1731. GC/MS *m/z* 239. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.32; H, 7.30; N, 5.70.
   Ethyl 4-Iodo-2-(1*H*-pyrrol-2-yl)butanoate (**7**): Iodide **9** was used to give 227 mg (74%) of **7** as an oil, homogeneous by TLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (b s, 1H), 6.75 (m, 1H), 6.15 (dd, J = 2.8, 5.9 Hz, 1H), 6.10 (m, 1H), 4.20 (m, 2H), 3.87 (dd, J = 6.5, 8.5 Hz, 1H), 3.19 (ddd, J = 6.1, 6.8, 9.8 Hz, 1H), 3.05 (ddd, J = 6.8, 7.9, 9.8 Hz, 1H), 2.44 (m, 1H), 2.29 (m, 1H), 1.29 (t, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 173.2, 126.7, 118.4, 108.8, 107.6, 61.7, 45.5, 37.0, 14.5, 3.5 GC *m/z* 307 (M^+); IR (neat) 1709 cm^{-1}. Anal. Calcd for $C_{10}H_{14}INO_2$:C, 39.11; H, 4.59; N, 4.56. Found: C, 39.47; H, 4.74; N, 4.27.
10. Methyl 5-oxo-5,6,7,8-tetrahydo-indolizidine-8-carboxylate (**5**): A 225-mg (1.00 mmol) portion of **3** was added to a 25-mL round-bottomed flask with 446 mg (3.00 mmol) of K_2CO_3 and 10 mL of DMF. The reaction mixture was deoxygenated with bubbling N_2 and was heated for 6 h under N_2. The crude reaction mixture was dissolved in 50 mL of brine and then extracted with four 30-mL portions of ether. The ether layers were combined and washed with three 30-mL portions of water, and the solvents were removed by rotary evaporation to give a dark brown oil. This crude product was further purified by MPLC with 15% EtOAc/85% hexane (v/v) to give 117 mg (60%) of **5** as a clear, colorless oil, homogeneous by TLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 1.5 Hz, 3.2 Hz, 1H), 6.28 (t, J = 3.3 Hz, 1H), 6.20 (m, 1H), 3.79 (s, 3H), 2.97 (m, 1H), 2.70 (m, 1H), 2.35 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 172.2, 167.8, 129.4, 117.4, 113.1, 111.7, 52.9, 39.4, 31.2, 24.9; IR (neat) 3448, 1726; GC/MS *m/z* 193. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.45; H, 5.81; N, 7.19.
11. Ethyl 3-oxo-dihydro-1*H*-pyrrolizine-1-carboxylate (**6**): A 239-mg (1 mmol) portion of **4** was dissolved in 150 mL of toluene, and 690 mg (5 mmol) of Na_2CO_3 was added. The reaction mixture was deoxygenated with bubbling N_2 and the resulting mixture was distilled to dryness under N_2. The residue was eluted through florisil with EtOAc, and solvents were removed by rotary evaporation. This crude product was further purified by MPLC with 15% EtOAc/85% hexane (v/v) to give 82 mg (43%) of **6** as a colorless oil, homogeneous by TLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 3.1 Hz, 1H), 6.47 (t, J = 3.1 Hz, 1H), 6.16 (m, 1H), 4.25 (m, 3H), 3.49 (dd, J = 18.6, 3.8 Hz, 1H), 3.19 (dd, J = 18.6, 8.6 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 170.4, 170.2, 136.6, 119.5, 112.3, 106.7, 62.3, 38.5, 38.1, 14.5; GC/MS *m/z* 193. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.03; H, 5.71; N, 7.21.
12. Ethyl 2,4-diiodobutyrate (**9**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51 (dd, J = 6.6, 8.1, 1H), 4.23 (m, 2H), 3.29 (dt, J = 10.1, 6.2 Hz, 1H) 3.19 (ddd, J = 6.6, 7.7 10.1 Hz)

2.41 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.0, 62.5, 38.9, 21.4, 14.2, 4.3; IR (neat) 1721 cm^{-1}.

13. Commercially available from Karl Industries, Aurora, OH.
14. Ethyl 1-(1H-Pyrrol-2-yl)-cyclopropanecarboxylate (**10**): Iodide **7** (1.33 g, 4.33 mmol) was dissolved in 20 mL of absolute EtOH. Triethylamine (0.61 mL, 4.33 mmol) was added, and the mixture was heated to reflux overnight. The solvents were removed by rotary evaporation, and the crude product was purified by MPLC in 10% ethylacetate/90% hexane (v/v) to give 631 mg (3.53 mmol, 81%) of **10** as an oil, homogeneous by TLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (b s, 1H), 6.76 (m, 1H), 6.13 (dd, $J = 2.7$, 6.0 Hz, 1H), 5.86 (m, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 1.67 (dd, $J = 4.0$, 7.3 Hz, 2H), 1.27 (dd, $J = 4.0$, 7.3 Hz, 2H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.3, 131.0, 117.6, 108.0, 104.8, 61.4, 22.2, 19.4, 14.6; GC/MS m/z 179 (M^+); IR (neat) 1721 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.72; H, 7.41; N, 7.62.

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