Cuprous bromide-promoted cyclization of ketene *N,S*-acetals with prop-2-ynyl bromide: synthesis of regiospecifically substituted and annelated 3-acyl(or nitro)-5-methyl pyrroles

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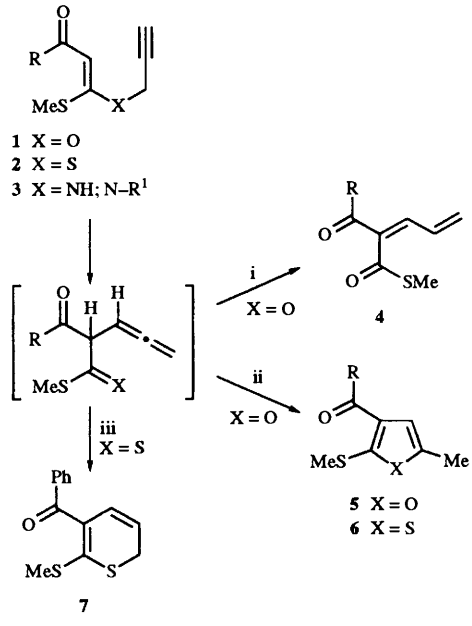
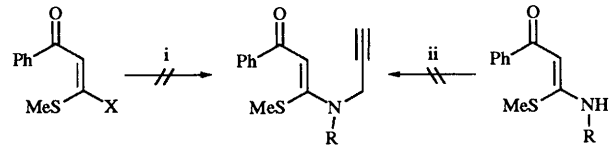
Acyclic **10a–h** and cyclic **14a–b** acyl and nitroketene **12a–b** *N,S*-acetals undergo facile cuprous bromide induced cyclization with prop-2-ynyl bromide to afford 1-substituted-3-acyl(or nitro)-5-methyl-2-(methylsulfanyl)pyrroles **11a–h** and **13a–b** and the corresponding annelated analogues **15a–b** in good yields.

Claisen rearrangement of suitable prop-2-ynyl ethers[1] and thioethers[1,2] are known for both aliphatic and aromatic compounds. The final products isolated in these rearrangements are generally pyran (or benzopyran) and furan (benzofuran) derivatives or the corresponding thio analogues (from thio-Claisen rearrangement). A few reports are available on the related acetylenic aza-Claisen rearrangement which usually require higher temperature or Lewis acid catalysis and afford either pyridine or quinoline derivatives.[3] In a recent paper, we described our studies on acetylenic oxa-Claisen rearrangement of oxoketene *O*-prop-2-ynyl *S*-methyl acetals to give either diene esters **4** (toluene heating) or the furans **5** (K_2CO_3/Et-COMe) depending on the reaction conditions.[4] Analogous thio-Claisen rearrangement of the corresponding *S*-prop-2-ynyl thioacetal **2** (R = Ph) (generated *in situ*) on the other hand yields the dihydrothiopyran **7** instead of 2-methylthiophene **6** (Scheme 1).[5] These rearrangements proceed rapidly under relatively mild conditions and thus suggested that the corresponding *N*-prop-2-ynyl *S*-methyl acetal **3** might also rearrange to either dihydropyridine or pyrrole derivatives. This prompted us to attempt synthesis of *N*-prop-2-ynyl *S*-methyl acetals **3** and study the reaction of *N,S*-acetals with prop-2-ynyl bromide under various conditions. Although we were not successful in synthesizing the intermediate **3**, the corresponding anticipated products of aza-Claisen rearrangement from **3**, *i.e.* 1-substituted-3-acyl-5-methyl-2-(methylsulfanyl)pyrroles **11**, could be obtained by cuprous bromide-promoted cyclization of *N,S*-acetals with prop-2-ynyl bromide. The results of these studies are described in this paper.



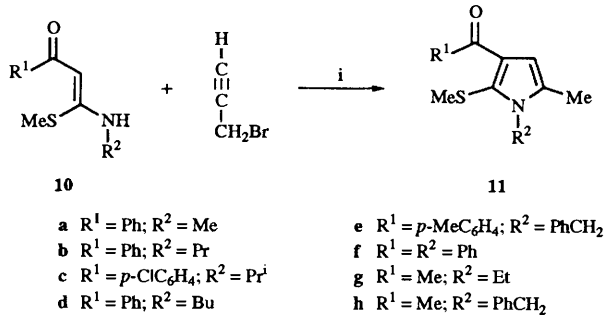
Scheme 1 *Reagents and conditions:* i, toluene, heat; ii, K_2CO_3, EtCOMe, heat; iii, KOBu^t, DMF



Scheme 2 *Reagents and conditions:* i, $HC{\equiv}CCH_2NH_2$; NaH, DMF; ii, $HC{\equiv}CCH_2Br$

Results and discussion

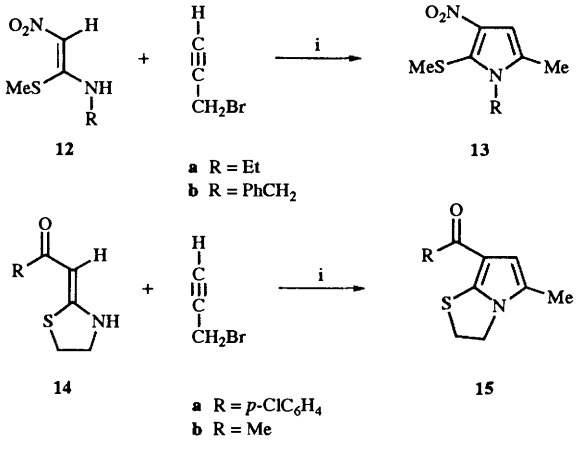
Attempted synthesis of the unsubstituted *N*-prop-2-ynyl *S*-methyl acetal **3a** by direct displacement on ketene *S,S*-acetal **8** or the corresponding sulfonium salt **9** by prop-2-ynylamine under different reaction conditions gave either starting material or an intractable mixture of products (Scheme 2). Similarly, our various trial experiments involving base-induced alkylation of *N,S*-acetal **10a** with prop-2-ynyl bromide to give either *N*-methyl-*N*-prop-2-ynyl *S*-methyl acetal **3b** or its subsequent rearrangement products resulted in failure. We therefore treated *N,S*-acetal **10a** with prop-2-ynyl bromide in the presence of various cuprous salts and copper catalysts. Best results were obtained with cuprous bromide and the product (63%) thus isolated was identified as 3-benzoyl-1,5-dimethyl-2-(methylsulfanyl)pyrrole **11a** on the basis of its spectral and analytical data. No trace of *N*-methyldihydropyridine or any other product of acetylenic aza-Claisen rearrangement was observed in the reaction mixture. The reaction was found to be general and other *N*-substituted aroyl **10b–f** and acetyl **10g–h** ketene *N,S*-acetals similarly afforded the corresponding pyrroles **11b–h** in moderate to good yields under identical conditions (Scheme 3). The reaction was equally facile with nitroketene *N,S*-acetals **12a–b** and the corresponding 5-methyl-3-nitropyrroles **13a–b** could be obtained in 57 and 81% yields, respectively (Scheme 4). The cyclic *N,S*-acetals **14a–b** also reacted with prop-2-ynyl bromide in a similar fashion under these conditions to afford annelated pyrroles **15a–b** in good yields.



10 **11**

a R^1 = Ph; R^2 = Me
b R^1 = Ph; R^2 = Pr
c R^1 = *p*-ClC_6H_4; R^2 = Pr^i
d R^1 = Ph; R^2 = Bu
e R^1 = *p*-MeC_6H_4; R^2 = $PhCH_2$
f R^1 = R^2 = Ph
g R^1 = Me; R^2 = Et
h R^1 = Me; R^2 = $PhCH_2$

Scheme 3 *Reagents and conditions:* i, Cu^{I}Br, dioxane, 100 °C



12 **13**

a R = Et
b R = $PhCH_2$

14 **15**

a R = *p*-ClC_6H_4
b R = Me

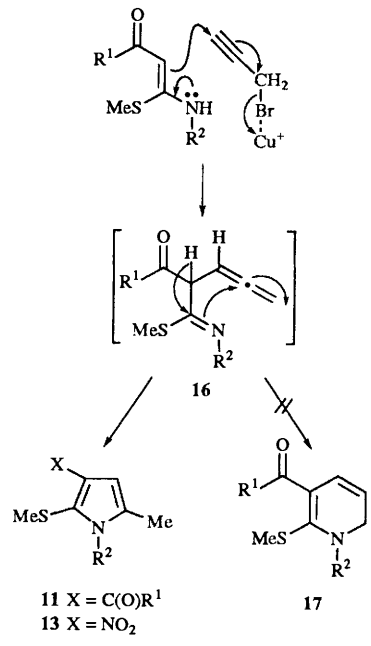
Scheme 4 *Reagents and conditions:* i, Cu^{I}Br, dioxane, 100 °C

The proposed mechanism for the formation of the pyrroles **11**, **13** and **15** is outlined in Scheme 5. Apparently, the reaction between *N*,*S*-acetals and prop-2-ynyl bromide is catalysed in the presence of Cu^{I}Br, since the reaction between *N*,*S*-acetals and prop-2-ynyl bromide was not observed in its absence, with few exceptions where only traces of the product pyrroles were formed. Subsequently, the allene intermediate **16** appears to undergo rapid cyclization by intramolecular nucleophilic attack of the amino group on the reactive allenic central carbon to afford the pyrroles.

The reaction provides a facile regiocontrolled synthesis of 1,2-substituted and annelated 3-acyl(or nitro)-5-methylpyrroles from easily accessible *N*,*S*-acetals, although the overall transformation does not appear to involve any aza-Claisen rearrangement.[6] Our efforts to synthesize substrates for aliphatic acetylenic aza-Claisen rearrangement and to probe the mechanism of their Lewis acid catalysis are in progress.

Experimental

Mps were determined on a Thomas Hoover melting point (capillary method) apparatus and are uncorrected. IR spectra were measured using a Perkin-Elmer 297 spectrometer. ^{1}H NMR (90 MHz) spectra were recorded on a Varian EM-390 spectrometer. High field ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini 300 BB spectrometer. Chemical shifts are reported in ppm relative to internal tetramethylsilane and *J* values in Hz. Mass spectra were measured on a JEOL JMS-D 300 mass spectrometer. Elemental analysis was carried out on a Heraeus CHN-O-Rapid Analyser. Dry dioxane was freshly distilled from sodium benzophenone ketyl prior to use.



11 X = C(O)R^1
13 X = NO_2

17

Scheme 5

General procedure for the preparation of 1,2,3-trisubstituted-5-methylpyrroles 11a–h, 13a–b and 15a–b

To a solution of prop-2-ynyl bromide (1.18 g, 10 mmol) in dry dioxane (30 ml) was added Cu^{I}Br (1.43 g, 10 mmol) in one portion. After the mixture had been stirred at ambient temperature for 0.5 h, the corresponding *N*,*S*-acetal (10 mmol) was added and heated under reflux for 4–6 h (monitored by TLC). The cold reaction mixture was poured into ice cold water (50 cm^3) and extracted with chloroform (2 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give crude pyrroles which were chromatographed on silica gel eluting with hexane–ethyl acetate (20:1).

3-Benzoyl-1,5-dimethyl-2-(methylsulfanyl)pyrrole 11a. Viscous oil (1.54 g, 63%); ν_{max}(neat)/cm^{-1} 1638 (CO); δ_H(90 MHz; CCl_4) 2.17 (3 H, s, CH_3), 2.33 (3 H, s, SCH_3), 3.63 (3 H, s, NCH_3), 6.03 (1 H, s, 4-H), 7.26–7.46 (3 H, m, ArH) and 7.66–7.80 (2 H, m, ArH); δ_C(75 MHz; $CDCl_3$), 13.03 (CH_3), 20.33 (SCH_3), 30.94 (NCH_3), 111.22, 127.94, 129.52, 131.47 (C-4, C-5', C-2', C-3', C-4' and C-6') and 131.01, 126.44, 128.05, 140.13 and 191.47 (C-2, C-3, C-5, C-1' and CO); *m*/*z* 245 (M^+, 100%), 230 (41) and 212 (65) (Found: C, 68.5; H, 6.15; N, 3.5. $C_{14}H_{15}NOS$ requires C, 68.54; H, 6.16; N, 5.71%).

3-Benzoyl-5-methyl-2-methylsulfanyl-1-propylpyrrole 11b. Viscous oil (1.34 g, 49%); ν_{max}(neat)/cm^{-1} 1638 (CO); δ_H(90 MHz; CCl_4) 0.96 (3 H, t, *J* 7, CH_2CH_3), 1.74 (2 H, distorted sext, *J* 7, CH_2CH_3), 2.23 (3 H, s, CH_3), 2.50 (3 H, s, SCH_3), 4.00 (2 H, t, *J* 7, NCH_2), 6.06 (1 H, s, 4-H), 7.26–7.53 (3 H, m, ArH) and 7.70–7.90 (2 H, m, ArH); *m*/*z* 273 (M^+, 100%), 258 (33) and 240 (72) (Found: C, 69.2; H, 6.5; N, 5.25. $C_{16}H_{19}NOS$ requires C, 70.29; H, 7.00; N, 5.12%).

3-(4-Chlorobenzoyl)-1-isopropyl-5-methyl-2-(methylsulfanyl)-pyrrole 11c. Viscous oil (2.43 g, 79%); ν_{max}(neat)/cm^{-1} 1647 (CO); δ_H(90 MHz; CCl_4) 1.53 [6 H, d, *J* 7, $CH(CH_3)_2$], 2.28 (3 H, s, CH_3), 2.35 (3 H, s, SCH_3), 5.14 [1 H, distorted sext, *J* 7, $CH(CH_3)_2$], 6.00 (1 H, s, 4-H), 7.30 (2 H, d, *J* 9, ArH) and 7.72 (2 H, d, *J* 9, ArH); *m*/*z* 308 (M^+, 25%), 307 (M^+, 100), 292 (22) and 274 (38) (Found: C, 62.3; H, 5.7; N, 4.7. $C_{16}H_{18}ClNOS$ requires C, 62.43; H, 5.89; N, 4.55%.

3-Benzoyl-1-butyl-5-methyl-2-(methylsulfanyl)pyrrole 11d. Viscous oil (1.46 g, 51%); ν_{max}(neat)/cm^{-1} 1642 (CO); δ_H(90 MHz; CCl_4) 0.96 (3 H, t, *J* 7, CH_3), 1.20–1.66 (4 H, distorted quint, *J* 7, 2 × CH_2CH_3), 2.20 (3 H, s, CH_3), 2.40 (3 H, s, SCH_3),

4.09 (2 H, t, *J* 7, NCH_2), 6.13 (1 H, s, 4-H), 7.41–7.56 (3 H, m, ArH) and 7.76–7.91 (2 H, m, ArH); *m/z* 287 (M^+, 47%), 272 (13) and 254 (34) (Found: C, 71.0; H, 7.35; N, 4.9. $C_{17}H_{21}NOS$ requires C, 71.04; H, 7.36; N, 4.67%).

1-Benzyl-5-methyl-3-(4-methylbenzoyl)-2-(methylsulfanyl)-pyrrole 11e. Viscous oil (2.15 g, 64%); ν_{max}(neat)/cm^{-1} 1688 (CO); δ_H(90 MHz; CCl_4); 2.10 (3 H, s, CH_3), 2.25 (3 H, s, CH_3), 2.40 (3 H, s, SCH_3), 5.34 (2 H, s, NCH_2), 6.14 (1 H, s, 4-H), 6.90 (2 H, d, *J* 9, ArH), 7.10–7.30 (5 H, m, ArH) and 7.73 (2 H, d, *J* 9, ArH); *m/z* 335 (M^+, 52%) and 302 (19) (Found: C, 75.1; H, 6.2; N, 4.4. $C_{21}H_{21}NOS$ requires C, 75.19; H, 6.31; N, 4.18%).

3-Benzoyl-5-methyl-2-methylsulfanyl-1-phenylpyrrole 11f. Colourless crystals (1.66 g, 54%); mp 118 °C (from chloroform–hexane); ν_{max}(KBr)/cm^{-1} 1638 (CO); δ_H(90 MHz; CCl_4), 2.05 (3 H, s, CH_3), 2.20 (3 H, s, SCH_3), 6.20 (1 H, s, 4-H), 7.13–7.33 (3 H, m, ArH), 7.34–7.56 (5 H, m, ArH) and 7.73–7.93 (2 H, m, ArH); *m/z* 307 (M^+, 100%), 292 (31) and 274 (78) (Found: C, 74.0; H, 5.3; N, 4.8. $C_{19}H_{17}NOS$ requires C, 74.23; H, 5.58; N, 4.56%).

3-Acetyl-1-ethyl-5-methyl-2-(methylsulfanyl)pyrrole 11g. Viscous oil (1.02 g, 52%); ν_{max}(neat)/cm^{-1} 1660 (CO); δ_H(90 MHz; CCl_4), 1.26 (3 H, t, *J* 7, CH_2CH_3), 2.21 (3 H, s, CH_3), 2.30 (3 H, s, CH_3CO), 2.34 (3 H, s, SCH_3), 4.06 (2 H, q, *J* 7, CH_2CH_3) and 6.20 (1 H, s, 4-H); *m/z* 197 (M^+, 100%), 182 (61) and 164 (63) (Found: C, 60.7; H, 7.5; N, 7.3. $C_{10}H_{15}NOS$ requires C, 60.87; H, 7.66; N, 7.10%).

3-Acetyl-1-benzyl-5-methyl-2-(methylsulfanyl)pyrrole 11h. Viscous oil (1.40 g, 54%); ν_{max}(neat)/cm^{-1} 1663 (CO); δ_H(90 MHz; CCl_4), 2.12 (3 H, s, CH_3), 2.16 (3 H, s, $COCH_3$), 2.44 (3 H, s, SCH_3), 5.33 (2 H, br s, CH_2), 6.36 (1 H, s, 4-H), 6.77–6.95 (2 H, m, ArH) and 7.16–7.34 (3 H, m, ArH); *m/z* 259 (M^+, 59%) and 226 (11) (Found: C, 69.2; H, 6.5; N, 5.25. $C_{15}H_{17}NOS$ requires C, 69.46; H, 6.61; N, 5.40%).

1-Ethyl-5-methyl-2-methylsulfanyl-3-nitropyrrole 13a. Viscous oil (1.14 g, 57%); ν_{max}(neat)/cm^{-1} 1500 and 1450; δ_H(90 MHz; CCl_4), 1.29 (3 H, t, *J* 7, CH_2CH_3), 2.24 (3 H, s, CH_3), 2.39 (3 H, s, SCH_3), 4.13 (2 H, q, *J* 7, CH_2CH_3) and 6.43 (1 H, s, 4-H); *m/z* 200 (M^+, 100%) and 153 (34) (Found: C, 47.8; H, 6.15; N, 14.0. $C_8H_{12}N_2O_2S$ requires C, 47.98; H, 6.04; N, 13.99%).

1-Benzyl-5-methyl-2-methylsulfanyl-3-nitropyrrole 13b. Viscous oil (2.12 g, 81%); ν_{max}(neat)/cm^{-1} 1505 and 1450; δ_H(90 MHz; CCl_4), 2.13 (3 H, s, CH_3), 2.26 (3 H, s, SCH_3), 5.35 (2 H, s, NCH_2), 6.55 (1 H, s, 4-H), 6.80–7.00 (2 H, m, ArH) and 7.14–7.34 (3 H, m, ArH); *m/z* 262 (M^+, 52%) (Found: C, 59.3; H, 5.3; N, 10.8. $C_{13}H_{14}N_2O_2S$ requires C, 59.52; H, 5.38; N, 10.68%).

7-(4-Chlorobenzoyl)-5-methyl-2,3-dihydropyrrolo[2,1-*b*]-thiazole 15a. Viscous oil (1.80 g, 65%); ν_{max}(neat)/cm^{-1} 1615 (CO); δ_H(90 MHz; CCl_4), 2.33 (3 H, s, CH_3), 3.23 (2 H, t, *J* 9, SCH_2), 4.33 (2 H, t, *J* 9, NCH_2), 6.26 (1 H, s, 4-H), 7.30 (2 H, d, *J* 9, ArH) and 7.96 (2 H, d, *J* 9, ArH); *m/z* 278 (M^+, 39%) and 276 (100) (Found: C, 60.35; H, 4.65; N, 5.3. $C_{14}H_{12}NOSCl$ requires C, 60.53; H, 4.36; N, 5.04%).

7-Acetyl-5-methyl-2,3-dihydropyrrolo[2,1-*b*]thiazole 15b. Viscous oil (1.03 g, 57%); ν_{max}(neat)/cm^{-1} 1615 (CO); δ_H(90 MHz; CCl_4), 2.20 (3 H, s, CH_3), 2.47 (3 H, s, CH_3CO), 3.22 (2 H, t, *J* 9, SCH_2), 4.24 (2 H, t, *J* 9, NCH_2) and 6.06 (1 H, s, 4-H); *m/z* 181 (M^+, 100%) and 121 (97.3) (Found: C, 59.4; H, 6.0; N, 8.0. $C_9H_{11}NOS$ requires C, 59.64; H, 6.12; N, 7.73%).

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