An Improved Coupling Procedure for the Barton-Zard Pyrrole Synthesis

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Received December 5, 2000

An improved final step in the Barton-Zard pyrrole synthesis uses inexpensive potassium carbonate as base in the coupling-cyclization reaction of *vic*-nitro-acetates with isocyanides. In this modification the isolated yields of synthetically useful 2-carboalkoxypyrroles (**1a**,**b** and **3**) and 2-(*p*-toluenesulfonyl)pyrroles (**2a**,**b**) consistently rise to the 78-89% range. Conversion of **2a** to 5-(*p*-toluenesulfonyl)-2-pyrrolinone **4** is conveniently and directly achieved by reaction with 30% hydrogen peroxide in acetic acid, thus circumventing the commonly used two step procedure involving bromination followed by solvolysis.

J. Heterocyclic Chem., **38**, 527 (2001).

Pyrrole 2-esters have been synthesized by a wide variety of methods, and with appropriate substituents and a hydrogen at C(5), they have proved to be important components in the syntheses of dipyrroles, porphyrins and their homologs, and linear oligopyrroles [1-3]. 5*H*-Pyrroles, such as **1a**, **1b** and **3** (Figure 1), are typically prepared from 5-methylpyrroles **5** and **6** by removal of the methyl group [4], *e.g.*, perchlorination to trichloromethyl, then hydrolysis to a carboxylic acid followed by decarboxylation. In order to improve the yields of 5*H*-pyrroles formed from pyrrole 5-carboxylic acids, the latter were decarboxylated in the presence of iodine, and the resulting 5-iodo pyrroles were de-iodinated by catalytic hydrogenolysis on palladium or platinum oxide [4c,e-j]. Thus, the benzyl ester of **5** has been converted to **1a** in 4 steps and an overall yield of 28% by the following transformations: (5-methyl, 2-carbobenzyloxy) → (5-carboxy, 2-carbobenzyloxy) → (5-carboethoxy, 2-carbobenzyloxy) → (5-carboethoxy, 2-carboxy) **1a** [4b]. Alternatively, rather than directly decarboxylating in the final step, (5-carboethoxy, 2-carboxy) was converted to (5-carboethoxy, 2-iodo) and then to **1a** in 43% overall yield [4c]. Similarly, pyrrole **5** was converted to **1b** by the sequence **5** (2-carboethoxy, 5-carboxy) **1b**; however, a yield was not cited [4d]. The conversion was also achieved *via* the iodopyrrole (2-carboethoxy, 5-iodo) in overall yields ranging from 38-49% [4e-g]. Synthesis of the more elaborate pyrrole **3** from **6** was achieved in overall yields of 43-86% by sequence: **6** (2-carbobenzyloxy, 5-carboxy) → (2-carbobenzyloxy, 5-iodo) **3**, where step 1 employed sulfuryl chloride and step 2 used iodine-potassium bicarbonate [4h-j].

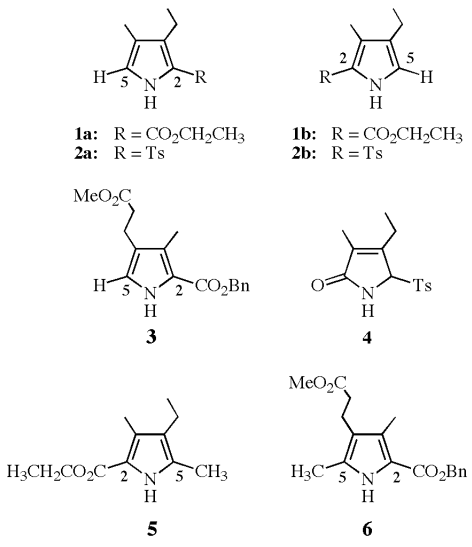


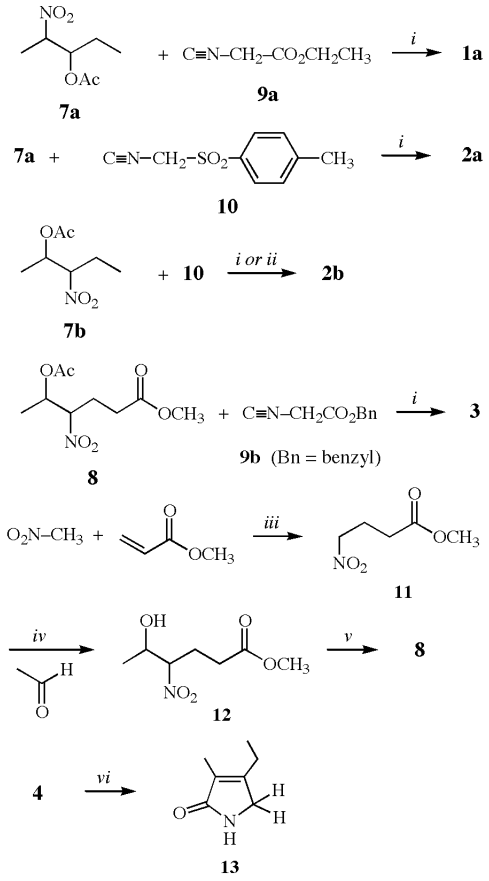
Figure 1. Pyrroles (**1-3**) formed from the Barton-Zard reaction or less directly from **5** and **6**. Pyrrolinone **4** is formed directly from **2a** by oxidation with hydrogen peroxide in acetic acid. Ts = *p*-toluenesulfonyl; Bn = benzyl.

More recently, **1a** and **3** have been synthesized directly and in fewer steps by pyrrole-forming cyclizations [5-7], including the Barton-Zard reaction [6] of the *vic*-nitroacetates (**7a** and **8**) with the required isocyanoacetate ester: **9a** to give **1a** [5c], **9b** to give **3** [7] in the presence of tetramethylguanidine (TMG) or 1,8-diazobicyclo[5.4.0]-undec-7-ene (DBU) (Scheme 1). Although no yield was cited for **1a** [5c], related cyclizations gave 38-47% yields [5a,b]. No reports have appeared for the synthesis of **1b** by the Barton-Zard reaction [6]; whereas, at least four such successful attempts have been published for the synthesis of **3** all using DBU as base, and all with yields 62-73% [7].

Similarly, the Barton-Zard method has been used to prepare δ-tosylpyrroles **2a** and **2b** in 53-55% yield by coupling the appropriate *vic*-nitro-acetate (**7a** → **2a**; **7b** → **2b**) with *p*-toluenesulfonylmethyl isocyanide (TosMIC, **10**) [8] using TMG as base (Scheme 1). α-Tosylpyrroles **2a** and **2b** have been shown to be very useful precursors to 3-methyl-4-ethyl-3-pyrrolin-2-one (**4**) [8-10] and 3-ethyl-4-methyl-3-pyrrolin-2-one [11], respectively, which are valuable components for the syntheses of dipyrrinones and linear tetrapyrroles related to bilirubin, biliverdin and phytochrome [1].

In view of the simplicity of the Barton-Zard procedure for forming (5*H*, 2-carboalkoxy) or (5*H*, 2-(*p*-toluenesulfonyl)) pyrroles for bile pigment and porphyrin synthesis, we explored methods to improve the product yield at the cyclization step while decreasing the reliance on TMG and DBU as bases. We found potassium carbonate to be a less expensive choice that usually afforded much higher yields than those previously published.

Scheme 1 [a]



[a] Reagents and conditions: *i*, tetramethylguanidine (TMG); *ii*, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); *iii* potassium carbonate; *iv*, potassium fluoride; *v*, acetic anhydride; *vi*, sodium borohydride

The precursor *vic*-nitro-acetates **7a** and **7b** are readily available from the Henry reaction coupling of nitroethane and propionaldehyde (to give the alcohol of **7a** in 80% yield) [8,12a] or of 1-nitropropane and acetaldehyde (to give the alcohol of **7b** in 78% yield) [12a] using potassium fluoride in 2-propanol. Conversion of the nitro-alcohols to the corresponding acetates (**7a** and **7b**) was achieved smoothly and in 90% yield [6,8]. Coupling **7a** with ethyl isocyanoacetate (**9a**) using DBU in acetonitrile from 0 °C to room temperature for 3 days afforded only a 27% isolated yield of **1a**; whereas, potassium carbonate in acetonitrile gave a 31% yield. With potassium carbonate and tetrahydrofuran-ethanol or tetrahydrofuran-isopropyl alcohol at room temperature for 3-5 days, a much improved yield (69-72%) of **1a** was obtained (Scheme 1). Our best yield (86%) was obtained when neat **7a** and neat **9a** were mixed and stirred with potassium carbonate containing tetra-*n*-butylammonium bromide, with the resulting solid mass being allowed to stand at room temperature for 3 days. Pyrrole **1b** was prepared in 78% yield using potassium carbonate in tetrahydrofuran-ethanol. In either **1a** or **1b**, the yields are higher than those reported previously using the Barton-Zard procedure with TMG or DBU as base [8,10,11], and they are much higher than those obtained by multistep conversion of **5**.

For the synthesis of **3**, nitromethane was coupled to methyl acrylate by a Michael reaction. Typically, the desired nitro-ester (**11**) is accompanied by the product of a second Michael addition (between methyl acrylate and **11**), which can be separated by distillation. With neat methyl acrylate and neat nitromethane, and solid potassium carbonate as base, a 60% isolated yield of pure **11** was obtained. Henry reaction of **11** with acetaldehyde gave nitro-alcohol **12** [12b] in 88% yield, and **12** was acetylated to afford **8** in 90% yield. A Barton-Zard type condensation of **8** with benzyl isocyanoacetate (**9b**) afforded an 88% yield of **3** (Scheme 1) using potassium carbonate as base. In tetrahydrofuran-methanol solvent (room temperature, 5 days) only the dimethyl ester of **3** was isolated (69% yield) due to transesterification. However, in tetrahydrofuran with 5% *tert*-butyl alcohol, an 88% yield of pure **3** was obtained.

The yields of tosylpyrroles **2a** and **2b** were also improved considerably by changing the base from TMG or DBU to potassium carbonate in the Barton-Zard condensation of **7a** and **7b**, respectively, with TosMIC (**10**) (Scheme 1). Our yield of **2a** from **7a** using TMG as base in tetrahydrofuran-isopropyl alcohol was 62% after reaction for 3 days at room temperature. With a change to potassium carbonate in tetrahydrofuran-isopropyl alcohol, the yield rose upwards to 86%. Changing the solvent to methanol gave only a 64% yield of **2a** using potassium carbonate, but with the combination of potassium carbonate in tetrahydrofuran-methanol (room temperature, 3 days) we isolated an 85-92% yield of **2a**. Conversion of **7b** to **2b** could be accomplished in a similarly high yield by the latter method.

Tosylpyrrole **2a** (Figure 1) is a useful precursor to pyrrolinone **13** (Scheme 1) [8-10]. In previous studies, **13** was prepared from **2a** by bromination at C(5) of the pyrrole ring using bromine [8] or phenyltrimethylammonium tribromide [10]. The resulting 2-tosyl-5-bromopyrrole was treated with trifluoroacetic acid and water to afford tosylpyrrolinone **4**, then the tosyl group was removed reductively using sodium borohydride. A shorter, more economical procedure for preparing tosylpyrrolinones involves treating the tosyl pyrrole with hydrogen peroxide in acetic acid. Thus, **2a** gave the corresponding tosylpyrrolinone (**4**) in 56% isolated yield, and **4** was converted to **13** in 88% yield by treatment with sodium borohydride in ethanol.

EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra were obtained in deuteriochloroform on a GE QE-300 spectrometer operating at 300

MHz (proton) and 75 MHz (C-13) in deuteriochloroform solvent. Chemical shifts are reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and the C-13 signal at 77.0 ppm. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Analytical thin layer chromatography was on J.T. Baker silica gel IB-F plates (125 µm layers). Flash column chromatography used silica gel, 60-200 mesh (M. Woelm). All solvents were reagent grade obtained from Fisher. Acetic acid, hydrogen peroxide, potassium fluoride, potassium carbonate and acetic anhydride were from Fisher. Nitromethane, methyl acrylate, acetaldehyde, tetra-*n*-butylammonium bromide, *p*-dimethylaminopyridine and sodium borohydride were purchased from Acros. Deuterated chloroform was from Cambridge Isotope Laboratories. *p*-Toluenesulfonylmethyl isocyanide (TosMIC) [13] and benzyl isocyanoacetate [7a] were prepared according to literature procedures. 2-Nitro-3-pentyl acetate (**7a**) and 3-nitro-2-pentyl acetate (**7b**), prepared according to literature procedures [6,12a]. Methyl 5-hydroxy-4-nitrohexanoate (**12**) was prepared in 88% yield as described previously [12]. Methyl 5-acetoxy-4-nitrohexanoate (**8**) [12b] was prepared in 90% yield by acetylation of **12** [6].

Ethyl 3-Ethyl-4-methyl-1*H*-pyrrole-2-carboxylate (**1a**).

A mixture of 2-nitro-3-pentyl acetate (**7a**) (1.75 g, 0.01 mole) and ethyl isocyanoacetate (**9a**) (1.13 g, 0.01 mole) was added in one portion with stirring to powdered potassium carbonate (2.9 g, 0.021 mole) containing tetra-*n*-butylammonium bromide (65 mg, 0.2 mmole). Stirring was continued for a few hours at room temperature until the mixture solidified. After standing for 3 days at room temperature, the solid material was triturated with anhydrous diethyl ether (4 x 50 ml). The ether solution was washed with water, then brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give an orange liquid, which was purified by column chromatography on silica gel using dichloromethane-methanol (99:1 by volume) to afford 1.56 g (86%) of **1a** [4a-c,5] as a yellow powder. It had mp 70-71 °C (lit. [4b] mp 75 °C); ^{1}H nmr: δ 8.67 (bs, 1H), 6.65 (d, 1H, J = 2.2 Hz), 4.31 (q, 2H, J = 7.2 Hz), 2.75 (q, 2H, J = 7.6 Hz), 2.04 (s, 3H), 1.35 (t, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.6 Hz). When the method employed for the preparation of **1b** was used, **1a** was isolated in 69% yield.

Ethyl 4-Ethyl-3-methyl-1*H*-pyrrole-2-carboxylate (**1b**).

3-Nitro-2-pentyl acetate (**7b**) (1.75 g, 0.01 mole) and ethyl isocyanoacetate (**9a**) (1.13 g, 0.01 mole) were added dropwise to a vigorously stirred suspension of potassium carbonate (2.9 g, 0.021 mole) in 30 ml of 1:1 (by volume) tetrahydrofuran-ethanol at room temperature over 20 minutes. The mixture was stirred at room temperature for 5 days then quenched by pouring into water (80 ml). The pH was adjusted to 6, and the mixture was extracted with diethyl ether (4 x 50 ml) and dried over anhydrous magnesium sulfate. The ether was then evaporated under reduced pressure to give an orange liquid, which was purified by column chromatography on silica gel, eluting with dichloromethane:methanol (99:1) to afford 1.41 g (78%) of **1b** [4d-g] as an orange oil (lit [4f] mp 22-23 °C). ^{1}H nmr: δ 8.84 (bs, 1H), 6.67 (d, 1H, J = 2.6 Hz), 4.31 (q, 2H, J = 7.1 Hz), 2.43 (q, 2H, J = 7.5 Hz), 2.29 (s, 3H), 1.35 (t, 3H, J = 7.1 Hz), 1.17 (t, 3H, J = 7.5 Hz).

3-Ethyl-4-methyl-2-(*p*-toluenesulfonyl)-1*H*-pyrrole (**2a**).

2-Nitro-3-pentyl acetate (**7a**) (1.75 g, 0.01 mole) was added dropwise to a vigorously stirred suspension of *p*-toluenesulfonylmethyl isocyanide (**10**) (TosMIC) (1.95 g, 0.01 mole) and potassium carbonate (2.9 g, 0.021 mole) in a 1:1 by volume mixture of tetrahydrofuran:methanol (30 ml) at room temperature over 20 minutes. The mixture was stirred at room temperature for 3 days. After cooling in an ice bath, the reaction was quenched with 30 ml of 5% hydrochloric acid added dropwise during 2 hours. The precipitated white product was collected by filtration, washed with water and dried under vacuum to afford 2.33 g (89%) of **1** [8,10,14]. It had mp 122-123 °C (lit [8] mp 114-116 °C); ^{1}H nmr: δ 8.96 (bs, 1H), 7.76 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 6.69 (d, 1H, J = 2.6 Hz), 2.61 (q, 2H, J = 7.5 Hz), 2.39 (s, 3H), 1.98 (s, 3H), 0.97 (t, 3H, J = 7.5 Hz).

4-Ethyl-3-methyl-2-(*p*-toluenesulfonyl)-1*H*-pyrrole (**2b**).

This pyrrole was prepared in 82% yield using the method above for 3-ethyl-4-methyl-2-(*p*-toluenesulfonyl)-1*H*-pyrrole (**2a**) [5c,11,14]. It had mp 116-117 °C (lit [5c] mp 117-118 °C; ^{1}H nmr: δ 8.85 (bs, 1H), 7.76 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 6.69 (d, 1H, J = 2.9 Hz), 2.40 (s, 3H), 2.35 (q, 2H, J = 7.6 Hz), 2.15 (s, 3H), 1.12 (t, 3H, J = 7.6 Hz).

Benzyl 4-(Methoxycarbonylethyl)-3-methyl-1*H*-pyrrole-2-carboxylate (**3**).

Methyl 5-acetoxy-4-nitrohexanoate (**8**) (2.33 g, 0.01 mole) and benzyl isocyanoacetate (**9b**) [7a] (1.77 g, 0.01 mole) were added dropwise to a vigorously stirred suspension of potassium carbonate (2.9 g, 0.021 moles) in a solvent mixture of tetrahydrofuran (19 ml) and *tert*-butyl alcohol (1 ml) at room temperature over 20 minutes. The mixture was stirred at room temperature for 5 days then quenched by pouring into water (60 ml). The pH was adjusted to 6, and the mixture was extracted with diethyl ether (4 x 20 ml). After drying over anhydrous magnesium sulfate, the ether was evaporated under reduced pressure to give a brown liquid, which was purified by column chromatography on silica gel using dichloromethane:methanol (99:1 to 95:5) as eluent to afford 2.65 g (88%) of **3** [4e,h-j,7] as a pale yellow oil (lit [4h] mp 41-42 °C); ^{1}H nmr: δ 8.83 (bs, 1H), 7.39-7.32 (m, 5H), 6.68 (d, 1H, J = 2.9 Hz), 5.29 (s, 2H), 3.66 (s, 3H), 2.75 (t, 2H, J = 7.7 Hz), 2.53 (t, 2H, J = 7.7 Hz), 2.30 (s, 3H).

Methyl 4-Nitrobutanoate (**11**).

Methyl acrylate (45.3 ml, 0.5 mole) was added dropwise to a vigorously stirred suspension of potassium carbonate (6.91 g, 0.05 mole) in nitromethane (270 ml, 5.0 moles) at room temperature over 20 minutes. The mixture was then stirred at room temperature for 12 hours. The potassium carbonate was removed by filtration and washed with chloroform (100 ml). The solvent, including excess nitromethane, was evaporated under reduced pressure to give a colorless liquid, from which **11** was obtained in 60% yield (44.1 g) as a colorless oil after distillation under reduced pressure, bp 80-82 °C at 0.5 mm Hg, (lit [15] bp 74-82 °C at 0.25 mm Hg). A by-product, dimethyl 4-nitro-1,7-heptanedioate, bp 140-150 °C at 0.5 mm Hg, was isolated as a viscous oil, 26.8 g (23%).

4-Ethyl-3-methyl-5-(*p*-toluenesulfonyl)-1,5-dihydro-1*H*-pyrrolin-2-one (**4**).

3-Ethyl-4-methyl-2-(*p*-toluenesulfonyl)pyrrole (**2a**) (25 g, 95 mmoles, 1 equivalent) was dissolved in glacial acetic acid (550 ml) at room temperature. After complete dissolution, hydrogen peroxide (30%, 14.6 ml, 142.5 mmoles, 1.5 equivalent) was

added slowly during 7 hours. The resulting mixture was stirred at room temperature for 19 hours then cooled in an ice bath while a saturated solution of sodium carbonate was added dropwise to pH ~8. The resulting yellow-white precipitate was collected by filtration and dried under reduced pressure to afford 14.48 g (56%) of **4**. It had mp 155-156 °C (lit [10] 154-155 C); ^{1}H nmr: δ 7.64 (d, 2H, J = 8.1 Hz), 7.30 (d, 2H, J = 8.1 Hz), 6.34 (bs, 1H), 5.15 (s, 1H), 2.75-2.49 (m, 2H), 2.43 (s, 3H), 1.58 (s, 3H), 1.20 (t, 3H, J = 7.5 Hz).

Acknowledgments.

We thank the National Institutes of Health (HD 17776) for support of this work.

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