# Facile Synthesis of 3-Alkylpyrroles

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## Introduction

Polypyrrole films are currently being explored in applications such as biosensors, addressable gene-chips, and interactive conduits for neuronal tissue engineering.[1] 3-Substituted alkylpyrroles have utility as functionalizable monomers for derivatization and modification of polypyrrole surfaces. 3-Alkyl pyrroles bearing reactive end groups on the alkyl moiety can be utilized to impart certain biospecificity, for example, by attachment of peptide ligands. Furthermore, 3-alkyl pyrroles are important synthetic intermediates. As the chemistry of 3-acyl pyrroles is well established,[2] 3-alkyl pyrroles are usually synthesized from corresponding acyl derivatives using the Clemmensen reduction.[3,4] However, the reduction conditions are too harsh for acid labile functionalities such as alkyl esters and the t-Boc protecting group.

We now report a facile five-step pathway to the synthesis of 4-(3-pyrrolyl)butanoic acid with every step being carried out under very mild reaction conditions with good to excellent yields. The reaction conditions can be easily modified to accommodate various pyrrole derivatives and might have broad application in synthetic organic chemistry.

## Results and Discussion

The most effective pathway to 3-substituted pyrroles requires introducing an electron-withdrawing group on the pyrrole nitrogen which drives subsequent Friedel−Crafts electrophilic substitution predominantly or exclusively on the $\beta$-carbon.[2,3] The most commonly used directing group is the phenylsulfonyl group. This is because phenylsulfonyl pyrrole (**1**) is easily synthesized either via the pyrrole−potassium salt or by using NaOH (solid or aqueous) in the presence of a phase-transfer catalyst. Furthermore, this directing group is easily removed under simple basic hydrolysis.[2,5]

Compound **1** was synthesized in 74% yield by overnight treatment of 1 equiv of pyrrole with 1.2 equiv of phenylsulfonyl chloride in dry dichloromethane in the presence of solid NaOH (3−5 equiv). To our knowledge this is the first report of the use of inorganic base in the sulfonylation of pyrrole nitrogen in an anhydrous organic solvent without a phase-transfer catalyst. Passing a concentrated solution of **1** in dichloromethane through an alumina column enabled rapid purification of the product.

Friedel−Crafts acylation of **1** using 3-carbomethoxypropionyl chloride has been reported by Kakushima et al.[3] Their conditions call for a 3-fold excess of acyl chloride in the presence of $AlCl_3$ added over 1.5 h to give methyl 4-[1-(phenylsulfonyl)-3-pyrrolyl)-4-butanoate (**2**) in 100% yield before purification. We found that such a high excess of the acyl chloride is not necessary. Using a 1.5-fold excess of the acyl chloride a 100% conversion was achieved after 2.5 h with a 90% yield of **2** after recrystallization.

Ketone intermediates are widely used to obtain $sp^3$ carbon centers. Sodium cyanoborohydride has been shown to be a mild, acid stable reducing agent of tosylhydrazones of ketones and aldehydes, including hindered systems, and thus to be an excellent alternative to the Clemmensen and Wolff−Kishner reductions.[6−8] Although reductive deoxygenation of aryl tosylhydrazones has been achieved in some cases using sodium borohydride, the reaction conditions are harsh and the yields are not optimum.[10] We report herein the reduction of a pyrrolyl alkyl ketone using the tosylhydrazone intermediate and sodium cyanoborohydride as the reducing agent under mild conditions to produce the corresponding alkyl derivative in high yield.

1-(Phenylsulfonyl)-3-pyrrolyl-2-carbomethoxyethyl ketone tosylhydrazone (**3**) was prepared by reaction of **2** with 1.2 equiv of *p*-toluenesulfonyl hydrazine in absolute ethanol in 90% yield after purification. Reduction of **3** was carried out in glacial acetic acid using 1:5 mole ratio of tosylhydrazone to sodium cyanoborohydride to yield methyl 4-[1-(phenylsulfonyl)-3-pyrrolyl]butanoate (**4**) in 75% yield after column chromatography.[11] Hydrolysis of **4** to 4-(3-pyrrolyl)butanoic acid (**5**) was then accomplished in 90% yield. The mp and IR spectra of **5** matched with the values reported in the literature.[12] The overall conversion of pyrrole to **5** was 40.5%. We have coupled **5** to hydroxy-terminated polymers under DCC/DMAP conditions to yield polymer-modified pyrroles. This is a subject of an ongoing investigation.

The reduction of aryl alkyl ketone tosylhydrazone in acetic acid is broad in its applicability as it is carried out at moderate temperature in almost neutral pH. TLC, IR, and $^1H$ NMR analyses of the crude reaction product revealed that the reduction of ketone tosylhydrazones by $NaBH_3CN$ in acetic acid at room-temperature proceeds

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(1) Shastri, V. R.; Pishko, M. V. Biomedical Applications of Electroactive Polymers. In *Electrical and Optical Polymer Systems*, Wise, D. L., Wnek, G. E., Trantolo, D. J., Cooper, T. M., Gresser, J. D., Eds.; Marcel Dekker: NY, 1998; p 1031.

(2) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, *4*, 353.

(3) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.

(4) Ryder, K. S.; Morris, D. G.; Cooper, J. M. *Langmuir* **1996**, *12* (23), 5681.

(5) Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1981**, *22*, *49*, 4899.

(6) Hutchins, R. O.; Milewski C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.

(7) Miller, V. P.; Yang, D.; Weigel, T. M.; Han, O.; Liy, H. *J. Org. Chem.* **1989**, *54*, 4175.

(8) Iida, T., Tamura, T., Matsumoto, T. *Synthesis* **1984**, 957.

(9) Miller et al.[7] reported that aryl ketones tosylhydrazones are readily converted to tosylhydrazine derivatives, but no attempts were made to obtain fully reduced hydrocarbon.

(10) Hutchins, R. O.; Natale N. R. *J. Org. Chem.* **1978**, *43*, 2299.

(11) We found that while scaling up the reaction the relative amount of solvent may be reduced by a factor of 2 and the ratio of tosylhydrazone: $NaBH_3CN$ to 1: 3.

(12) Kamogawa, H.; Nakata, T.; Ohori, S.; Komatsu, S.; *Bull. Chem. Soc. Jpn.* **1991**, *64*, 4 (3), 1066.

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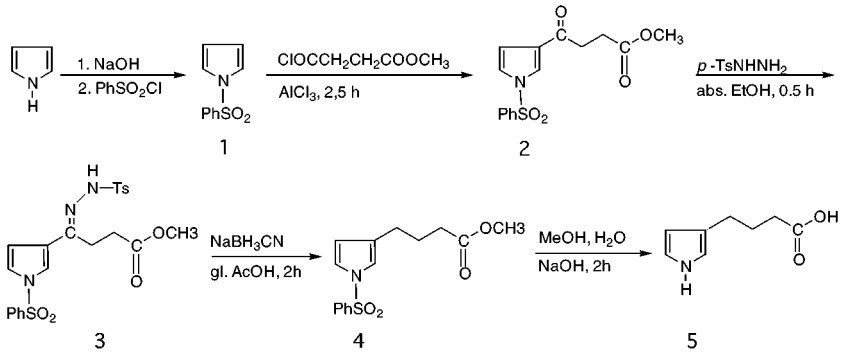
**Scheme 1**




free of side reactions and is compatible with labile protecting groups such as alkyl esters.

## Experimental Section

All chemicals were purchased and used as received except pyrrole, which was purified prior to use by passing through an activated alumina (EM Science, 80−235 mesh) column until colorless. Melting points were determined on a Fisher-Johns melting point apparatus. IR spectra were obtained on a Fourier transform infrared spectrometer, and $^1$H NMR were recorded at 360 MHz in $CDCl_3$ solvent (Spectral Data Services, Inc.; Champaign, IL). Elemental analyses were carried out by Quantitative Technologies Inc. (Whitehouse, NJ). Chromatography was performed using Aldrich silica gel, and TLC was performed on Baker Flex silica gel 1B plates.

**(Phenylsulfonyl)pyrrole (1).** Pyrrole (9.7 g, 0.144 mol) was added to a well-agitated suspension of NaOH (17.3 g, 0.433 mol) in 100 mL of dichloroethane. This mixture was then cooled to 0 °C and stirred for 10 min, following which a solution of phenylsulfonyl chloride (30.5 g, 0.173 mol) in 20 mL of dichloroethane was added dropwise over a period of 20 min. Thirty minutes after the completion of addition, the reaction was allowed to come to room temperature and left stirring overnight. The reaction was quenched by pouring onto 300 mL of distilled water. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extract was washed with distilled water to neutrality and dried over $Na_2SO_4$. Removal of the solvent in vacuo gave **1** (22.0 g, 74%) as white crystalline solid. This solid was subsequently purified by passing a concentrated solution in dichloromethane through an alumina column in greater than 70% overall yield: mp 87−88 °C; IR (KBr): 3130, 1580, 1535, 1455, 1370, 1170, 1100, 730 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.30 (2H, t), 7.17 (2H, t), 7.50 (2H, t), 7.60 (1H, t); 7.85 (2H, m). Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 58.13; H, 4.23; N, 6.64; S, 15.56.

**Methyl 4-[1-(Phenylsulfonyl)-3-pyrrolyl]-4-butanoate (2).** To a suspension of $AlCl_3$ (10.8 g, 81 mmol) in 50 mL of 1,2-dichloroethane was added in portions 3-carbomethoxypropionyl chloride (6.1 g, 40.6 mmol), and mixture was stirred at 0 °C. After complete solubilization of aluminum chloride, a solution of **1** (5.6 g, 27.1 mmol) in 20 mL of same solvent was added dropwise with cooling. The mixture was allowed to stir for 2.5 h at room temperature after which time the reaction was quenched by pouring onto ice-cold water (300 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extract was washed with 10% sodium bicarbonate, then with water to neutrality and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure resulted in a dark oil, from which **2** (7.8 g, 90%) was then recrystallized (ethyl acetate/hexanes) as colorless needles: mp 74−76 °C; IR (KBr): 3150, 1740, 1680, 1375, 1175, 1100, 730 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.70 (2H, t); 3.09 (2H, t); 3.68 (3H, s); 6.8−7.6 (8H, m). Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36; S, 9.98. Found: C, 56.02; H, 4.55; N, 4.22; S, 10.18.

**1-(Phenylsulfonyl)-3-pyrrolyl-2-Carbomethoxyethyl Ketone tosylhydrazone (3).** *p*-Toluenesulfonylhydrazine (5.2 g, 28 mmol) and **2** (7.5 g, 23.4 mmol) were added to 9 mL of absolute ethanol. The mixture was refluxed for 30 min during which time a dense precipitate formed. The precipitate was separated, thoroughly washed with cold ether and dried under vacuum to give **3** as a white solid (10.3 g, 90%): mp: 161−163 °C; IR (KBr): 3220, 1745, 1600, 1375, 1335, 1170, 810, 730 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 2.40 (3H, s); 2.62 (2H, t); 2.72 (2H, t); 3.60 (3H, s); 6.5−8.0 (12H, m); 9.65 (1H, s). Anal. Calcd for $C_{22}H_{23}N_3O_6S_2$: C, 54.09; H, 4.54; N, 8.60; S, 13.13. Found: C, 54.07; H, 4.61; N, 8.51; S, 13.10.

**Methyl 4-[1-(Phenylsulfonyl)-3-pyrrolyl)]butanoic Acid (4).** Sodium cyanobohydride (0.6 g, 10 mmol) was added to a solution of **3** (1 g, 2 mmol) in 15 mL of glacial acetic acid, and the reaction mixture was allowed to stir at 40 °C for 2 h. Reaction was quenched by pouring onto 60 mL of ice-cold water, and the mixture was thoroughly extracted with ether. Combined organic extracts were washed with sodium bicarbonate and water to neutrality and dried over $Na_2SO_4$. Removal of the solvent resulted in the crude product, which was then purified by chromatography on a silica gel column (eluent 1:8 ethyl acetate−hexanes) to yield **4** as a white crystalline solid (0.5 g, 75%): mp 44−46 °C; IR (KBr) 3150, 1740, 1370, 1175, 1100, 735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 1.85 (2H, q); 2.28 (2H, t); 2.43 (2H, t); 3.65 (3H, s); 6,1−7,9 (8H, m). Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56; S, 10.43. Found: C, 58.76; H, 5.59; N, 4.39; S, 10.65.

**4-(3-Pyrrolyl)butanoic Acid (5). 4** (0.6 g, 2 mmol) was placed in 12 mL of 2:1 (v:v) mixture of MeOH and 5 N aqueous NaOH and refluxed for 1.5 h, after which time the reaction mixture was allowed to cool and methanol was removed in vacuo. The aqueous solution was acidified with 5 N HCl to pH 3 and thoroughly extracted with ethyl ether. Combined organic extracts were washed with water to neutrality and dried over $Na_2SO_4$. Removal of the solvent in vacuo yielded **5** (0.3 g, 90%) as a beige solid: mp 91−93 °C (lit. mp 89−91 °C); IR (KBr): 3400−2500, 3400, 2920, 1700, 1435, 1345, 1230, 1200, 1075 cm$^{-1}$.

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