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Facile synthesis of *N*-(arylsulfonyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrolle-2,3-dicarboxylates by one-pot three-component reaction

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Abstract

Three-component reaction of arylsulfonamides, dialkyl acetylenedicarboxylates, and ethyl chlorooxoacetate promoted by triphenylphosphine and triethylamine provides a sufficient route for the synthesis of dialkyl *N*-(arylsulfonyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrolle-2,3-dicarboxylates in good yields.

Keywords: Arylsulfonamides; Dialkyl acetylenedicarboxylates; Triphenylphosphine; Multi-component reactions; 3-Pyrollin-2-ones

Five-membered ring lactams have successfully been used in routes to various alkaloids [1,2] and are suitable precursors for unusual β-amino acids such as statine and its analogues [3,4]. There are also many examples of pyrroline-containing natural products with pharmacological activities. Typical examples are the antitumor alkaloide Jatropham and the platelet aggregation inhibitor PI-091[5]. *N*-Substituted 3-pyrrolines are important compounds which exhibit neuritogenic activity [6] and serve as useful synthetic intermediates [7–9]. Despite their wide applicability, available routes for the synthesis of 3-pyrrolin-2-ones are limited [10,11].

Sulfonamide-containing compounds have a high potential as pharmaceutical and agricultural agents due to their diverse biological profiles. The ability to serve as amide surrogates, with unique physical properties, have made them ideal functional groups for the development of novel peptidomimetics [12]. In addition, sulfonamides have served as key functional groups in the development of novel nonpeptidal HIV protease inhibitors [13], matrix metalloproteinase inhibitors, thrombin inhibitors and fibrinogen receptor antagonists [14].

Three-component addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylates (DAAD's) and arylsulfonamides has been reported to produce sulfur-containing iminophosphoranes **4** (Scheme 1) [15–18].

Recently, we reported the reaction of dialkyl acetylenedicarboxylates, triphenylphosphine, with primary amines in the presence of ethyl chlorooxoacetate for the synthesis of dialkyl *N*-aryl-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylates [19]. We also reported one-pot synthesis of polysubstituted pyrrole derivatives by three-component reaction between DAAD's, aromatic amines, triphenylphosphine and arylglyoxals [20].

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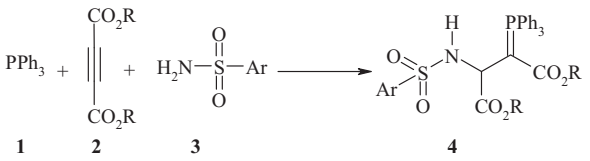
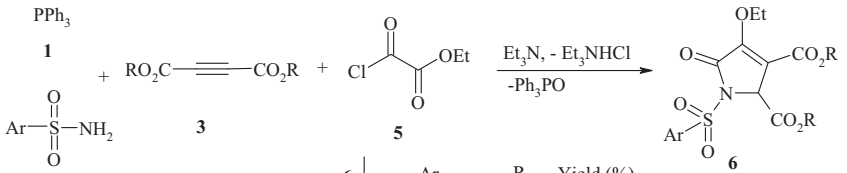


Scheme 1. Synthesis of sulfur-containing iminophosphoranes by reaction of PPh_3-DAAD zwitterion with arylsulfonamides.



6	Ar	R	Yield (%)
a	*p*-CH_3-pheny	Me	88
b	*p*-CH_3-pheny	Et	80
c	phenyl	Me	85
d	phenyl	Et	80
e	*p*-CH_3-pheny	*t*-Bu	60

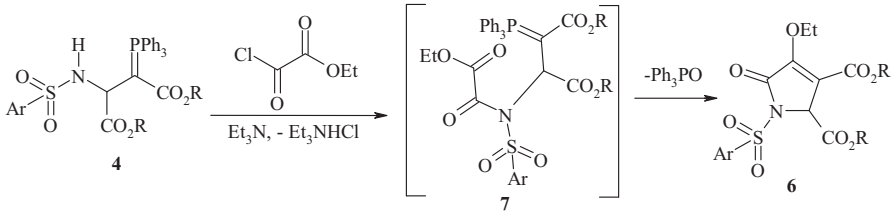
Scheme 2. Three-component reaction between arylsulfonamides, DAAD's, triphenylphosphine and ethyl chlorooxoacetate.

Here we report an extention of this route for the synthesis of dialkyl *N*-(arylsulfonyl)-4-ethoxy-5-oxo-2,5-dihydro-1*H*-pyrolle-2,3-dicarboxylates by three-component reaction of arylsulfonamides, DAAD's, triphenyl-phosphine and ethyl chlorooxoacetate in the presence of triethylamine (Scheme 2).

1. Results and discussion

The structures of compounds **6a–e** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. For example, the mass spectrum of **6a** displayed the molecular-ion peak at *m*/*z* 397. The 500 MHz ^{1}H NMR spectrum of **6a** exhibited three sharp signals at δ 2.43, 3.79 and 3.81 for three methyl group's protons. A triplet at 1.37 (J = 7 Hz) and a quartet at 4.60 were observed for ethyl protons. The proton of methine group of pyrroline ring resonated as a singlet at 5.30. The aromatic protons were observed at 7.33 and 7.97 (d, J = 8.2 Hz). The ^{13}C NMR spectrum of compound **6a** showed 15 distinct resonances in agreement with the proposed structure. The structural assignments made on the basis of the NMR spectra of compound **6a** were supported by its IR spectrum. The carbonyl groups exhibited strong absorption bands at 1745 and 1679 cm^{-1}.

It is rational to assume compounds **6a–e** are produced from the initial production of ylide **4** from three-component reaction of arylsulfonamides **2,** DAAD (**3**) and triphenylphosphine, which then reacted with ethyl chlorooxoacetate **5** to produce oxamate **7** that underwent intramolecular Wittig reaction to produce products **6** (Scheme 3).



Scheme 3. Suggested mechanism for formation of 3-pyrollin-2-one **6**.

2. Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

2.1. General procedure

To a magnetically stirred solution of PPh_3 (1 mmol) and arylsulfonamides derivative (1 mmol) in CH_2Cl_2 (10 mL) was added dropwise a mixture of DAAD (1 mmol) in CH_2Cl_2 (3 mL) at room temperature over 2 min. The reaction mixture was then stirred for one more min. triethylamine (1 mmol) and ethyl chlorooxoacetate (1 mmol) was added and the reaction mixture was stirred for more 24 h. Solvent was evaporated and the residue was purified by column chromatography on SiO_2 using EtOAc-hexane (1:4) mixture as eluent.

Dimethyl 4-ethoxy-2,5-dihydro-5-oxo-1-tosyl-1H-pyrrole-2,3-dicarboxylate ***(6a):*** Viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 1745 (2 C=O), 1679 (C=O, amide). Anal. Calcd. (%) for $C_{17}H_{19}NO_8S$: C, 51.38; H, 4.82; N, 3.52. Found: C, 51.42; H, 4.79; N, 3.54. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (t, 3H, $^{3}J_{HH}$ = 7 Hz, CH_3), 2.43 (s, 3H, CH_3), 3.79 and 3.81 (2s, 6H, 2 OCH_3), 4.60 (m, 2H, OCH_2), 5.30 (s, 1H, CH), 7.33 and 7.97 (2d, 4H, $^{3}J_{HH}$ = 8.2 Hz, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.91 and 22.17 (2 CH_3), 52.76 and 53.86 (2 OCH_3), 59.46 (OCH_2), 69.30 (CH), 115.80, 126.84, 129.17, 131.32, 134.61 and 146.46 (aromatic and olefinic carbons), 161.97, 162.785, 168.05 (3 C=O). MS, *m/z* (%) = 397(M^+, 16).

Diethyl 4-ethoxy-2,5-dihydro-5-oxo-1-tosyl-1H-pyrrole-2,3-dicarboxylate ***(6b):*** Viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 1723 (2 C=O, ester), 1641 (C=O, amide). Anal. Calcd. (%) for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.45; N, 3.29. Found: C, 53.79; H, 5.52; N, 3.34 ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01, 1.14 and 1.25 (t, 9H, $^{3}J_{HH}$ = 7 Hz, 3×CH_3), 2.36 (s, 3H, CH_3), 3.96, 4.12 and 4.22 (m, 6H, 3×OCH_2), 5.35 (s, 1H, CH), 7.26 and 7.91 (2d, 4H, $^{3}J_{HH}$ = 8.2 Hz, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.24, 14.52, 15.71 and 22.15 (4 CH_3), 59.86, 61.76 and 64.84 (3 OCH_2), 68.59 (CH), 113.12, 126.88, 129.18, 130.17, 133.60 and 146.66 (aromatic and olefinic carbons), 161.42, 163.51, 168.22 (3 C=O). MS, *m/z* (%) = 425 [M^+, 22].

Dimethyl-1-benzenesulfonyl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate ***(6c):*** Viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 1722, 1703 (2 C=O, ester), Anal. Calcd. (%) for $C_{16}H_{17}NO_8S$: C, 50.13; H, 4.47; N, 3.65. Found: C, 50.23; H, 4.52; N, 3.52. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, 3H, $^{3}J_{HH}$ = 7 Hz, CH_3), 3.70, 3.75 (s, 6H, 2×OCH_3), 4.23 (q, 2H, $^{3}J_{HH}$ = 7 Hz, OCH_2), 5.24 (s, 1H, CH), 7.46 (t, 2H, $^{3}J_{HH}$ = 7.7 Hz, 2CH of Ph), 7.58 (t, 1H, $^{3}J_{HH}$ = 7.5 Hz, CH of Ph), 8.02 (d, 2H, $^{3}J_{HH}$ = 7.6 Hz, 2CH of Ph). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.50 (CH_3), 52.81, 53.88, 59.50 (2 OCH_3 and OCH_2), 69.38 (CH), 115.90, 129.06, 129.53, 135.18, 137.96 and 152.32 (aromatic and olefinic carbons), 161.95, 162.81, 167.98 (3 C=O). MS, *m/z* (%) = 383 [M^+, 11].

Diethyl-1-benzenesulfonyl-4-ethoxy-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate ***(6d):*** Viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 1730, 1699 (2 C=O, ester), Anal. Calcd. (%) for $C_{18}H_{21}NO_8S$: C, 52.55; H, 5.14; N, 3.40. Found: C, 52.74; H, 5.23; N, 3.67, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (m, 9H, 3×CH_3), 4.19, 4.26 and 4.56 (m, 6H, 3×OCH_2), 5.28 (s, 1H, CH), 7.52 (t, 2H, $^{3}J_{HH}$ = 7.7 Hz, 2CH of Ph), 7.64 (t, 1H, $^{3}J_{HH}$ = 7.5 Hz, CH of Ph), 8.03 (d, 2H, $^{3}J_{HH}$ = 7.6 Hz, 2CH of Ph). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.34, 14.41 and 15.82 (3 CH_3), 59.75, 61.92 and 63.18 (3 OCH_2), 69.32 (CH), 116.32, 129.08, 129.44, 135.06, 137.72 and 152.16 (aromatic and olefinic carbons), 161.35, 162.89, 167.39 (3 C=O). MS, *m/z* (%) = 411 [M^+, 10].

Di-tert-butyl 4-ethoxy-2,5-dihydro-5-oxo-1-tosyl-1H-pyrrole-2,3-dicarboxylate ***(6e):*** Viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 1730, 1699 (2 C=O, ester), Anal. Calcd. (%) for $C_{23}H_{31}NO_8S$: C, 57.36; H, 6.49; N, 2.91. Found: C, 57.22; H, 6.70; N, 2.81, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, 3H, $^{3}J_{HH}$ = 7 Hz, CH_3), 1.34 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 2.43 (s, 3H, CH_3), 4.32 (q, 3H, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 5.23 (s, 1H, CH), 7.33 and 7.97 (d, 4H, $^{3}J_{HH}$ = 8.1 Hz, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.79, 21.70 ($2CH_3$), 27.52, 27.96 ($2C(CH_3)_3$), 65.83 (OCH_2), 64.37. (CH), 82.21, 83.18 (2C $(CH_3)_3$), 115.12, 126.40, 128.73,129.72, 134.49 and 153.64 (aromatic and olefinic carbons), 162.21, 164.01, 166.92 (3 C=O). MS, *m/z* (%) = 481 [M^+, 16].

3. Conclusion

In conclusion here we report the reaction between dialkyl acetylenedicarboxylates, arylsulfonamides and ethyl chlorooxoacetate promoted by triphenylphosphine and triethylamine, to produce functionalized 3-pyrrolin-2-one derivatives in high yields. The present method carries the advantage that not only is the reaction performed under simple conditions but also that the substances can be mixed without any activation or modification.

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