SYNTHESIS OF SOME FURYL- AND THIENYLACRYLATES OR DIACRYLATES AND ACRYLIC ACIDS BY THE PALLADIUM CATALYSED VINYLATION OF SUBSTITUTED BROMOFURANS AND BROMOTHIOPHENES

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Abstract - Furyl- and thienylacrylates (8-14) and acrylic acids (8a,10a-14a) are prepared in moderate yields by palladium catalysed coupling of substituted bromofurans and bromothiophenes with ethyl acrylate.

Our continuing interest in the synthesis and photochemistry of heterocyclic acrylic acids or substituted heterocyclic acrylic acids1-5 has prompted us to develop a synthetic method for the preparation of new furyl- and thienylacrylates (8,9,10 and 12) substituted with carboxy substituent either in the position 4 or 5 of the heterocyclic nucleus or with o-chloroanilido substituent attached to the position 5 of the furan nucleus. Diethyl 5-carboxy-2,3-furandiacrylate (11), diethyl 5-carboxy-2,3-thiophenediacrylate (13) and diethyl 2,5-thiophenediacrylate (14) have also been prepared by palladium catalysed coupling of bromofurans and bromothiophenes with ethyl acrylate. Corresponding acids (8a,10a-14a) have been prepared from previously obtained esters.

Palladium catalysed coupling of bromo or iodo substituted aromatic compounds with vinyl substituted reagents (ethyl acrylate, acrylonitrile, styrene, vinyl methyl ketone) is a well known and usefull reaction for the preparation of vinyl substituted aromatic compounds.6-11 There has been however, only one article reporting on the Heck reaction of heterocyclic carboxylic acids.12
### Table 1

Heck Reactions of Bromofurans and Bromothiophenes with Ethyl Acrylate

<table>
<thead>
<tr>
<th>Bromo derivative</th>
<th>Product</th>
<th>Yield %</th>
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<tbody>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>80</td>
</tr>
<tr>
<td>Cl-C(=O)-Br</td>
<td>Cl-C(=O)COOCH$_2$CH$_3$</td>
<td>40</td>
</tr>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>47</td>
</tr>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>51</td>
</tr>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>62</td>
</tr>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>55</td>
</tr>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>85</td>
</tr>
<tr>
<td>HOOC-C(=O)-Br</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>HOOC-C(=O)COOCH$_2$CH$_3$</td>
<td>85</td>
</tr>
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The ordinary Wittig reaction used for preparing aromatic or heterocyclic compounds substituted by vinyl or substituted vinyl group does not always give the good yields in heterocyclic series. Besides, the products are always a mixture of cis- and trans-isomers. On the other hand the preparation of the o-disubstituted diacrylates requires a multistep synthesis.\textsuperscript{13}

Palladium catalysed acrylation (vinylation) is a more convenient reaction and the yield ranges from 40-88\%.\textsuperscript{6-12}

The vinylation of all bromo compounds (1-7) was investigated under standard Heck conditions. These consisted of heating an acetonitrile solution of bromo compound with an excess of ethyl acrylate and triethylamine in the presence of 1\% palladium(II) acetate and 2-6\% of triphenylphosphine at 100°C for 12-20 hours. The results are summarized in Table 1. Moderate yields of yellow crystalline products (8-14 and 8a-14a) were obtained.

The stereochemistry of the double bond in the acrylates (8,9,10,12) and in the diacrylate (14) was exclusively trans as shown by the $J_H$ of 16 Hz from one or two olefinic doublets in the relevant $^1$H nmr spectra. It is important to emphasize that the stereochemistry of the double bonds was exclusively trans. However, the vinylic hydrogen atoms A' and B' in the acrylate attached to the position 3 of the heterocyclic nucleus are shifted in relation with vinylic hydrogen atoms A and B.

**EXPERIMENTAL**

Mps were determined on a Kofler hotstage microscope and are uncorrected. Ir spectra were recorded on a PERKIN-ELMER Model 257 spectrophotometer in KBr discs or as a liquid film between sodium chloride plate. $^1$H nmr spectra were recorded on a VARIAN M360 (60MHz) or on VARIAN GEMINI 300 (300MHz) with TMS as internal standard in CDCl$_3$ or DMSO-d$_6$.

5-Bromo-2-furancarboxylic Acid (1)

Compound (1) was prepared by bromination of 2-furancarboxylic acid (100 g, 0.892 mol) with Br$_2$ (146.4 g, 0.916 mol) in acetic acid (200 ml) on 90-100°C. White crystals, 59.2 g (34.8\%), mp 188-190°C, were obtained (lit.,\textsuperscript{14} mp 185°C).

5-Bromo-2-furyl-(p-chloro)anilide (2)

Compound (2) was prepared by the method\textsuperscript{15} described earlier from p-chloroaniline
(6.25 g, 0.05 mol) and 5-bromo-2-furoyl chloride (10 g, 0.048 mol) in pyridine (24 ml) and toluene (100 ml). Yellow crystals, 10.4 g (72%), mp 117°C, were obtained (lit.,15 mp 117°C).

5-Bromo-3-furancarboxylic Acid (3)
Compound (3) was prepared from 3-furancarboxylic acid (2.02 g, 0.018 mol) dissolved in glacial acetic acid (10 ml) where N-bromosuccinimide (3.2 g, 0.018 mol) was added by stirring at room temperature, and stirring continued for 24 h. The solvent was evaporated, residue extracted with ether leaving behind succinimide, and the ether solution distilled off. The residual oil was triturated with water and the resultant solid crystallized from water; yield 1.34 g (39%), mp 137-138°C (lit.,16 mp 136°C).

4,5-Dibromo-2-furancarboxylic Acid (4)
Compound (4) was prepared from 2-furancarboxylic acid (20 g, 0.178 mol) and dry bromine (99.5 g, 0.623 mol) which was added dropwise into the acid during 2 h on the room temperature. The mixture was heated to 100-110°C with stirring during 24 h, allowed to cool somewhat, 100 ml of water were added and the mixture was refluxed 17 h. Upon cooling the product precipitated as a brown solid which was recrystallized from water; yield 9.7 g (20.2%), mp 172°C (lit.,17 mp 168-170°C).

5-Bromo-2-thiophenecarboxylic Acid (5)
Compound (5) was prepared by bromination (12.4 g, 0.05 mol of bromine) of thiophene-2-carboxylic acid (10 g, 0.078 mol) in acetic acid (100 ml) at 0°C. White crystals, 7.56 g (47%), mp 135-136°C, were obtained (lit.,18 mp 141-142°C).

4,5-Dibromo-2-thiophenecarboxylic Acid (6)
Compound (7) was prepared from 2-thiophenecarboxylic acid (2.6 g, 0.020 mol) which was added into the bromine (19.2 g, 0.120 mol) with stirring. After standing overnight most of the excess bromine was evaporated the mixture was dissolved in 5% ammonium carbonate solution to remove the excess of bromine. The aqueous solution acidified with diluted HCl precipitate was filtered off and recrystallized from ethanol. White crystals, 2.24 g (42.0%), mp 227-228°C, were obtained (lit.,19 mp 225-227°C).
2,5-Dibromothiophene (7)

Compound (7) was prepared from 2-bromothiophene (19 g, 0.119 mol in 30 ml CC14) by adding bromine (19.3 g, 0.121 mol in 30 ml CC14) dropwise during 8 h, at room temperature. After stirring overnight, the solvent was removed in vacuo, 3.5 g of sodium hydroxide were added, mixture was heated on 100°C for 4 h, cooled, filtered and distilled; yield 20.5 g (73.8%). Yellow oil, bp 193-204°C (lit., bp 211°C).

Ethyl 3-(5-Carboxy-2-furyl)acrylate (8)

To the solution of palladium(I1) acetate (0.07 g, 0.31 mmol) and triphenylphosphine (0.33 g, 0.26 mol) in acetonitrile (50 ml) and triethylamine (11 ml) was added 1 (4.0 g, 0.21 mol) and ethyl acrylate (6.3 g, 0.063 mol). The reaction mixture was sealed in the glass tube and heated at 100°C for 20 h. The mixture was cooled, the content of the tube was evaporated in vacuo and the residue dissolved in water, filtered, filtrate boiled with charcoal acidified with diluted HCl, precipitate filtered off and recrystallized from ethanol; yield 3.6 g (82%), mp 139°C. Ir (cm⁻¹): 1710 (COOEt), 1660 (COOH), 1640 (C=C). ¹H Nmr (DMSO-d₆) (δ ppm): 7.50 (d, J=15.0 Hz, 1H, H_B), 7.35 (d, J=3.4 Hz, 1H, H_J), 7.14 (d, J=3.4 Hz, 1H, H_A), 6.40 (d, J=15.0 Hz, 1H, H_A), 4.30 (q, J=7.2 Hz, 2H, CH₂), 1.36 (t, J=7.2 Hz, 3H, CH₃). Anal. Calcd for C₁₁H₁₀O₂: C, 57.14; H, 4.76. Found: C, 57.07; H, 4.76.

3-(5-Carboxy-2-furyl)acrylic Acid (8a)

Acid (8a) was prepared by hydrolysis of 8 (3.6 g, 0.017 mol) dissolved in 100 ml ethanol, which was added to the solution of sodium hydroxide (2.73 g, 0.068 mol) in water (50 ml) and refluxed for 0.5 h. Ethanol was distilled off in vacuo, the residue dissolved in water and acidified with conc. HCl, precipitate filtered off and recrystallized from ethanol. Yellow crystals, 3 g (78%), mp 267-269°C were obtained. Ir (cm⁻¹): 1680 (COOH), 1640 (C=C). ¹H Nmr (DMSO-d₆) (δ ppm): 7.50 (d, J=15.0 Hz, 1H, H_B), 7.35 (d, J=3.4 Hz, 1H, H_J), 7.12 (d, J=3.4 Hz, 1H, H_A), 6.41 (d, J=15.0 Hz, 1H, H_A). Anal. Calcd for C₈H₆O₃: C, 53.35; H, 3.36. Found: C, 52.97; H, 3.70.

Ethyl 3-[5-(o-Chloroanilido)-2-furyl]acrylate (9)

Compound (9) was prepared from 2 (6.3 g, 0.021 mol) and ethyl acrylate (6.3 g, 0.063 mol)
as described above. After reaction was over and solvent distilled off the residue was washed with water and recrystallized from ethanol (150 ml). Yellow crystals, 2.7 g (34.8%), mp 120-122° C were obtained. IR (cm⁻¹): 1710 (COOEt), 1675 (CONH), 1640 (C=C).

₁H Nmr (CDCl₃) (δ ppm): 8.75 (s, 1H, NH), 8.52 (dd, J=8.3 Hz, J=1.4 Hz, 1H, H arom.), 7.48 (d, Jₐ,₉=15.8 Hz, 1H, H₉), 7.44 (dd, J=8.1 Hz, J=1.4 Hz, 1H, H arom.), 7.33 (dt, J=7.4 Hz, J=1.6 Hz, 1H, H arom.), 6.76 (d, J₃,₄=3.7 Hz, 1H, H₃), 6.47 (d, Jₐ,₉=15.8 Hz, 1H, H₉). Anal. Calcd for C₁₆H₁₇O₄N: C, 66.89; H, 5.92. Found: C, 66.53; H, 5.60.

Ethyl 3-(4-Carboxy-2-furyl)acrylate (10)

Compound (10) was prepared from 3 (3.9 g, 0.02 mol) as described for 8. Yellow crystals recrystallized from diluted methanol, 2 g (47%), mp 194-196° C were obtained. IR (cm⁻¹): 1670 (COOEt), 1630 (C=O), 1620 (C=C). ₁H Nmr (CDCl₃) (δ ppm): 8.11 (s, 1H, H₅), 7.41 (d, Jₐ,₉=15.8 Hz, 1H, H₉), 6.93 (s, 1H, H₃), 6.40 (d, Jₐ,₉=15.8 Hz, 1H, H₉). 4.26 (q, J=7.1 Hz, 2H, CH₂). Anal. Calcd for C₁₀H₁₀O₅: C, 57.14; H, 4.76. Found: C, 57.35; H, 4.39.

3-(4-Carboxy-2-furyl)acrylic Acid (10a)

Acid (10a) was prepared by hydrolysis of 10 (2.1 g, 0.01 mol) by the method described above. Precipitate was recrystallized from methanol, 1.35 g (75%) yellow powder, mp 320° C was obtained. IR (cm⁻¹) 1680 (COO), 1620 (C=C). ₁H Nmr (DMSO-d₆) (δ ppm): 12.87 (s, 2H, COOH), 8.53 (s, 1H, H₅), 7.53 (d, Jₐ,₉=16.0 Hz, 1H, H₉), 7.28 (s, 1H, H₃), 6.35 (d, Jₐ,₉=16.0 Hz, 1H, H₃). Anal. Calcd for C₈H₆O₅: C, 53.35; H, 3.36. Found: C, 53.03; H, 3.70.

Diethyl 5-Carboxy-2,3-furandiacrylate (11)

Compound (11) was prepared from 4 (5.67 g, 0.021 mol) as described for 8. Yellow crystals recrystallized from ethanol, 3.27 g (50.5%), mp 189-192° C, were obtained. IR (cm⁻¹): 1720 (COOEt), 1710 (COOH), 1620 (C=C). ₁H Nmr (CDCl₃) (δ ppm): 7.67 (d, Jₐ,B=15.9 Hz, 1H, H₉), 7.65 (d, Jₐ,B=15.6 Hz, 1H, H₉), 7.48 (s, 1H, H₄), 6.71 (d, Jₐ,B=15.9 Hz, 1H, H₉), 6.33 (d, Jₐ,B=15.6 Hz, 1H, H₉), 4.30 (q, J=7.1 Hz, 2H,
5-Carboxy-2,3-furandiacrylic Acid (11a)

Diacid (11a) was prepared by hydrolysis of 11 (1.5 g, 0.005 mol) by the method described above. Yellow crystals, recrystallized from DMSO-water 3:1, 1.01 g (80%), mp 315° were obtained. IR (cm⁻¹): 1710 (COOH), 1670 (COOH), 1625 (C=C). ¹H NMR (DMSO-d₆) (δ ppm): 7.92 (s, 1H, H₄), 7.77 (d, J₃,₄=15.6 Hz, 1H, H₅), 7.74 (d, J₃,₄=15.8 Hz, 1H, H₆). Anal. Calcd for C₁₅H₁₆O₇: C, 58.44; H, 5.23. Found: C, 58.02; H, 5.07.

Ethyl 3-(5-Carboxy-2-thienyl)acrylate (12)

Compound (12) was prepared from 5 (4.3 g, 0.021 mol) as described for 8. Yellow crystals, 5.9 g (62.3%), mp 88-93°C, were obtained. IR (cm⁻¹): 1715 (COOEt), 1693 (COOH), 1620 (C=C). ¹H NMR (CDCl₃) (δ ppm): 7.79 (d, J₃,₄=4.0 Hz, 1H, H₄), 7.73 (d, J₉,₁₀=15.8 Hz, 1H, H₉), 7.64 (d, J₃,₄=4.0 Hz, 1H, H₅), 6.38 (d, J₉,₁₀=15.8 Hz, 1H, H₉), 4.27 (q, J=7.1 Hz, 2H, CH₂), 1.34 (t, J=7.1 Hz, 3H, CH₃). Anal. Calcd for C₁₀H₁₀O₄S: C, 53.04; H, 4.42. Found: C, 53.38; H, 4.03.

3-(5-Carboxy-2-thienyl)acrylic Acid (12a)

Acid (12a) was prepared by hydrolysis of 12 (2.7 g, 0.015 mol) with NaOH as described for 8a. Yellow crystals recrystallized from ethanol, 2.3 g (77.5%), mp 264-266°C, were obtained. IR (cm⁻¹): 1680 (COOH), 1660 (COOH), 1610 (C=C). ¹H NMR (DMSO-d₆) (δ ppm): 7.73 (d, J₉,₁₀=15.9 Hz, 1H, H₉), 7.69 (d, J₃,₄=3.9 Hz, 1H, H₄), 7.55 (d, J₃,₄=3.9 Hz, 1H, H₅), 6.38 (d, J₉,₁₀=15.9 Hz, 1H, H₉). Anal. Calcd for C₈H₆O₄S: C, 48.48; H, 3.05. Found: C, 48.83; H, 3.45.

Diethyl 5-Carboxy-2,3-thiophenediacrylate (13)

Compound (13) was prepared from 6 (2.09 g, 0.007 mol) and ethyl acrylate (4.2 g, 0.042 mol) as described for 8. Yellow crystals, 1.26 g (55.5%), mp 145°C were obtained. IR (cm⁻¹): 1720 (COOEt), 1710 (COOEt), 1680 (COOH), 1620 (C=C). ¹H NMR (DMSO-d₆) (δ ppm): 8.30 (s, 1H, H₄), 8.05 (d, J₉,₁₀=15.0 Hz, 1H, H₉), 7.85 (d, J₉,₁₀=15.8 Hz, 1H, H₉), 6.83 (d, J₉,₁₀=15.6 Hz, 1H, H₉). 6.59 (d, J₉,₁₀=15.8 Hz, 1H, H₉), 4.33 (q, J=7.1 Hz, 2H, CH₂),
4.32 (q, J=7.1 Hz, 2H, CH₂), 1.38 (t, J=7.1 Hz, 6H, CH₃). Anal. Calcd for C₁₅H₁₆O₆S: C, 55.55; H, 4.97. Found: C, 55.13; H, 5.07.

5-Carboxy-2,3-thiophenediacrylic Acid (13a)

Diacid (13a) was obtained by hydrolysis of 13 (0.24 g, 0.75 mmol) with NaOH (0.14 g, 3.45 mmol) as described above. Yellow crystals, 0.18 g (90%), mp 292-294°C, were obtained. IR (cm⁻¹), 1680 (COOH), 1620 (C=C). H NMR (CDCl₃) (δ ppm): 8.24 (s, 1H, H₄), 7.99 (d, J=15.6 Hz, 1H, H_B), 6.71 (d, J=15.6 Hz, 1H, H_B), 6.51 (d, J=15.6 Hz, 1H, H_A). Anal. Calcd for: C₁₁H₈O₆S: C, 49.26; H, 3.01. Found: C, 49.60; H, 3.43.

Diethyl 2,5-Thiophenediacrylate (14)

Compound (14) was prepared from 7 (4.5 g, 0.018 mol) and ethyl acrylate (9.3 g, 0.093 mol) as described for 8. The crude product was chromatographed on a SiO₂ column with dichloromethane: cyclohexane 1:1 as eluent. Yellow crystals, 4.4 g (84.7%), mp 99-101°C were obtained. IR (cm⁻¹): 1710 (COOEt), 1695 (COOEt), 1620 (C=C). H NMR (CDCl₃) (δ ppm): 7.6 (d, J=15.2 Hz, 2H, H_B, H_B'), 7.1 (s, 2H, H₂, H₄), 6.11 (d, J=15.0 Hz, 2H, H_A, H_A'), 4.24 (q, J=8.0 Hz, 4H, CH₂), 1.32 (t, J=8.0 Hz, 6H, CH₃). Anal. Calcd for C₁₄H₁₆O₄S: C, 59.99; H, 5.75. Found: C, 59.50; H, 5.37.

2,5-Thiophenediacrylic Acid (14a)

Diacid (14a) was obtained by hydrolysis of 14 (1.85 g, 0.007 mol) with NaOH (1.7 g, 0.043 mol) as described above. Yellow crystals, 1.4 g (95%), mp 310°C were obtained.


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