4-Alkoxy-6-alkyl-2-pyrones as Precursors for 4-Alkoxy-6-alkyl-2-aminobenzoic Acid Derivatives[1]

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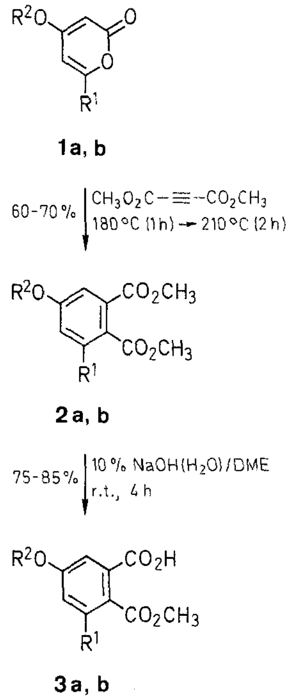
4-Alkoxy-6-alkyl-2-pyrones undergo Diels-Alder reaction with dimethyl acetylenedicarboxylate to give dimethyl 4-alkoxy-6-alkylphthalates, which can be converted into 4-alkoxy-6-alkyl-2-aminobenzoic esters via a simple two-step sequence.

Anthranilic acids (2-aminobenzoic acids) are valuable precursors for the synthesis of various heterocycles,[2-5] many of which are of medicinal interest.[6,7] The ability to manipulate substituents on the aromatic nucleus (e.g., of such acids) is important for chemical studies and for the investigation of structure-activity relationships in medicinal chemistry.[8] We report here a convenient procedure for the synthesis of 4,6-disubstituted anthranilic acid derivatives starting from 4-alkoxy-6-alkyl-2-pyrones **1**. The starting materials are either commercially available or readily prepared by known procedures.[9-12] The aromatic system of phthalic esters **2** is constructed using the Diels-Alder reaction between pyrones **1** and dimethyl acetylenedicarboxylate[12] (180–210 °C, for 3 h). The phthalates **2** can be hydrolysed selectively in 10% sodium hydroxide/1,2-dimethoxyethane (DME) at room temperature to give the mono-esters **3**. These are first treated with 1,1-carbonyldiimidazole in tetrahydrofuran for 2 h at room temperature to yield the azolides, which are then treated with azidotrimethylsilane at 110 °C in toluene to give the intermediate isocyanates **4** via Curtius rearrangement.[13,14] Reaction of not isolated isocyanates[4] with hydrochloric acid, ethanol, or isopropylamine affords the various anthranilic acid derivatives **5**, **6**, and **7**, respectively, which can be easily isolated by conventional means.



The scope of this reaction is broad since R^1 can be alkyl, aryl, or a heterocyclic moiety. Other substituted pyrones may be used as the diene in the Diels-Alder reaction.[15,16] The pyrone Diels-Alder reaction compares favourably with the use of 1,3-silyloxydienes[6] for the preparation of **2**. For instance, the Diels-Alder reaction between 2,4-bis(trimethylsiloxy)-1,3-pentadiene and dimethyl acetylenedicarboxylate, followed by acid hydrolysis and *O*-methylation, resulted in a poor yield of **2a**.[6] The ease of prepration of pyrones **1** has made the pyrone Diels-Alder approach very attractive. However, the substituents R^1 and OR^2 may both be required for the regioselective hydrolysis of the diesters **2** to the mono-esters **3**.

The Diels-Alder adducts **3** can easily be converted into anthranilic acid derivatives in a two-pot operation. Compounds **6** and **7** are convenient starting materials for the preparation of heterocycles. For example, treatment of **6** and **7** with concentrated sulphuric acid gives 4*H*-3,1-benzoxazin-4-ones **8** and **9**, respectively.[17] These benzoxazin-4-ones are inhibitors of human leukocyte elastase,[6,18] an enzyme implicated in the pathophysiology of emphysema and chronic inflammatory diseases.[7,8] The biochemical studies of these heterocycles will be reported elsewhere.

Dimethyl 4-Methoxy-6-methylphthalate (2a); Typical Procedure:

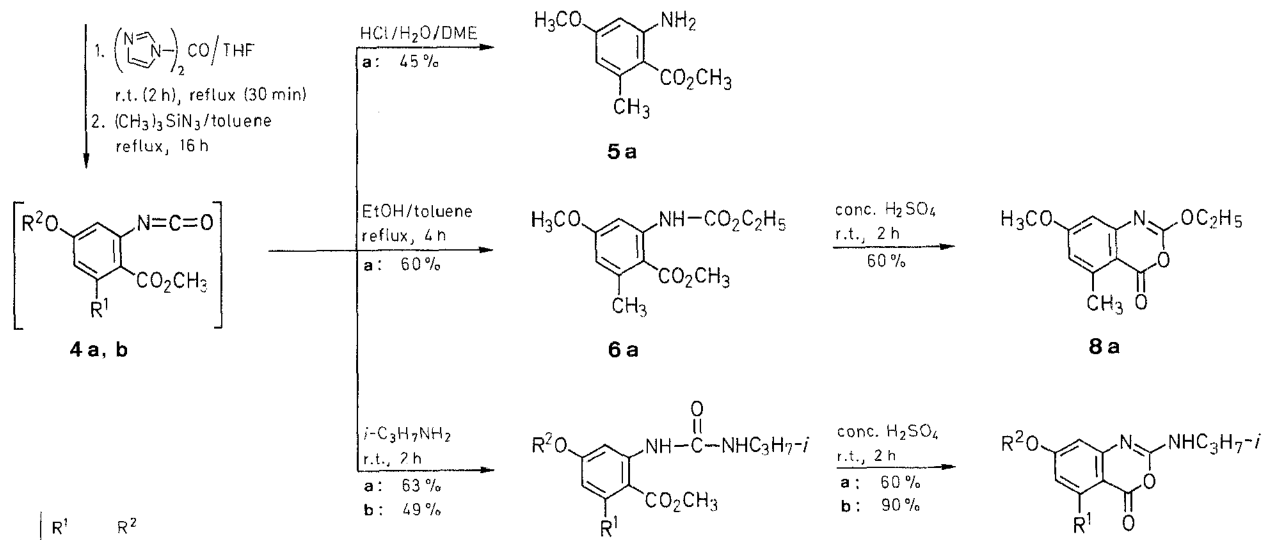
A mixture of dimethyl acetylenedicarboxylate (6.6 g, 46.4 mmol) and 4-methoxy-6-methyl-2-pyrone (**1a**; 4 g, 31.7 mmol) is heated in an oil bath at 180 °C for 1 h and then at 210 °C for 2 h. The mixture is cooled and the brown residue dissolved in CH_2Cl_2 (~ 10 mL). This material is purified by column chromatography [Whatman LPS-2 silica gel, elution gradient: 10 → 30% EtOAc in petroleum ether (bp 30–60 °C)] to give **3a** as an oil; yield: 5.1 g (66%); R_f 0.25 [15% EtOAc/petroleum ether (bp 30–60 °C).

MS (70 eV): m/z = 238 (M^+), 207 (M^+ $-OCH_3$); 179 (M^+ $-CO_2CH_3$), 164, 148.

5-Methoxy-2-methoxycarbonyl-3-methylbenzoic Acid (3a); Typical Procedure:

A solution of dimethyl 4-methoxy-6-methylphthalate (**2a**; 2.2 g, 9.23 mmol) in 8% aqueous NaOH (12 mL) + DME (12 mL) is stirred at room temperature for 4 h. The solvent is removed under reduced pressure and the aqueous solution is washed with EtOAc (3 × 125 mL). The organic extract is dried ($MgSO_4$) and evaporated to give a solid which is recrystallized from EtOAc/petroleum ether (bp 30–60 °C) to give **3a**; yield: 1.64 g (79%); mp 146–147 °C.

$C_{11}H_{12}O_5$	calc.	C 58.93	H 5.39
(224.2)	found	58.94	5.41



	R^1	R^2
a	CH_3	CH_3
b	C_2H_5	n-C_3H_7

Table. Compounds 2–9 Prepared

Compound	Yield (%)	Molecular Formula[a]	mp (°C)	IR[b] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J(Hz)
2a	66	$C_{12}H_{14}O_5$ (238.2) [MS: m/z = 238 (M^+)]	oil	1720, 1600	2.29 (s, 3H, CH_3); 3.78, 3.83, 3.86 (3s, 9H, $2CO_2CH_3$, OCH_3); 6.84 (br d, 1H_{arom}); 7.23 (d, 1H, J = 2.4, 1H_{arom})
2b	65	$C_{15}H_{20}O_5$ (280.3) [MS: m/z = 280 (M^+)]	oil	1725, 1600	1.02 (t, 3H, CH_3); 1.20 (t, 3H, CH_3); 1.78 (m, 2H, $C\underline{H}_2CH_2O$); 2.62 (q, 2H, CH_2Ar); 3.86, 3.88 (2s, 6H, $2OCH_3$); 3.90 (m, 2H, OCH_2); 6.95 (d, 1H, J = 2.5, 1H_{arom}); 7.30 (d, 1H, 1H_{arom})
3a	79	$C_{11}H_{12}O_5$ (224.2)	146–147	2500–3200, 1740, 1690	2.35 (s, 3H, CH_3); 3.86, 3.90 (2s, 6H, OCH_3, CO_2CH_3); 6.96 (br d, 1H_{arom}); 7.39 (d, 1H, J = 2.6, 1H_{arom}); 8.25 (br s, 1H, CO_2H)
3b	65	$C_{14}H_{18}O_5$ (266.3)	99–100	3650–3350, 1740, 1725, 1690	1.05 (s, 3H, $C\underline{H}_3CH_2CH_2$); 1.23 (s, 3H, $C\underline{H}_3CH_2$); 1.80 (m, 2H, $C\underline{H}_2CH_2O$); 2.65 (q, 2H, CH_2Ar); 3.86 (s, 3H, OCH_3); 3.98 (t, 2H, OCH_2); 7.00 (d, 1H_{arom}); 7.40 (d, 1H, J = 2.5, 1H_{arom}); 8.90 (br s, 1H, CO_2H)
5a	45	$C_{10}H_{13}NO_3$ (195.2)	95–96	3460, 3340, 1660, 1600	2.45 (s, 3H, CH_3); 3.78, 3.88 (2s, 6H, CO_2CH_3, OCH_3); 5.45 (br s, 2H, NH_2); 6.00 (d, 1H_{arom}); 6.10 (d, 1H, J = 2.6, 1H_{arom})
6a	60	$C_{13}H_{17}NO_5$ (267.3)	85–86	1730, 1665	1.30 (t, 3H, $C\underline{H}_3CH_2$); 2.50 (s, 3H, CH_3); 3.85, 3.90 (2s, 6H, CO_2CH_3, OCH_3); 4.20 (q, 2H, $CH_3C\underline{H}_2$); 6.30 (br d, 1H, J = 2.6, 1H_{arom}); 7.90 (d, 1H_{arom}); 9.90 (s, 1H, NH)
7a	63	$C_{14}H_{20}N_2O_4$ (280.3)	149–150	1690, 1650	1.20 [d, 6H, $CH(C\underline{H}_3)_2$]; 2.40 (s, 3H, CH_3); 3.80, 3.86 (2s, 6H, CO_2CH_3, OCH_3); 4.10 [m, 1H, $C\underline{H}(CH_3)_2$]; 6.40 (d, 1H, J = 2.6, 1H_{arom}); 7.96 (d, 1H_{arom}); 9.90 (br s, 1H, NH)
7b	49	$C_{17}H_{26}N_2O_4$ (322.4)	130–131	1690, 1650	1.00 (t, 3H, $C\underline{H}_3CH_2CH_2$); 1.22 [d, 6H, $CH(C\underline{H}_3)_2$]; 1.25 (t, 3H, $C\underline{H}_3CH_2$); 1.75 (m, 2H, $CH_3C\underline{H}_2CH_2O$); 2.80 (q, 2H, CH_2Ar); 3.78 (s, 3H, CO_2CH_3); 3.90 [m, 1H, $C\underline{H}(CH_3)_2$]; 3.94 (t, 2H, OCH_2); 4.50 (m, 1H, NH); 6.40 (d, 1H_{arom}); 7.85 (d, 1H, J = 2.5, 1H_{arom}); 9.40 (br s, 1H, NH)
8a	68	$C_{12}H_{13}NO_4$ (235.2)	138–140	1760, 1650	1.40 (t, 3H, $C\underline{H}_3CH_2$); 2.70 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 4.50 (q, 2H, OCH_2); 6.70 (s, 2H_{arom})
9a	60	$C_{13}H_{16}N_2O_3$ (248.2)	145–147	1740, 1630	1.20 [d, 6H, $CH(C\underline{H}_3)_2$]; 2.70 (s, 3H, CH_3); 3.90 (s, 3H, OCH_3); 4.15 [m, 1H, $C\underline{H}(CH_3)_2$]; 4.70 (br d, 1H, NH); 6.50 (s, 2H_{arom})
9b	90	$C_{16}H_{22}N_2O_3$ (290.4)	130–131	1720, 1645	1.00 (t, 3H, $C\underline{H}_3CH_2CH_2$); 1.20 (t, 3H, $C\underline{H}_3CH_2$); 1.22 [d, 6H, $CH(C\underline{H}_3)_2$]; 1.82 (m, 2H, $CH_2C\underline{H}_2CH_3$); 3.18 (q, 2H, CH_2Ar); 3.98 (t, 2H, $OC\underline{H}_2CH_2$); 4.70 (br s, 1H, NH); 6.56 (s, 2H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.08, N ±0.28.

[b] IR spectra of all solid samples were recorded as KBr pellet. IR spectra of **2a** and **2b** were recorded as film.

Methyl 2-Amino-4-methoxy-6-methylbenzoate (5a):

1,1-Carbonyldiimidazole (0.904 g, 5.58 mmol) is added to a stirred solution of 5-methoxy-2-methoxycarbonyl-3-methylbenzoic acid (**3a**; 1 g, 4.46 mmol) in THF (100 mL) under argon. The resulting solution is stirred at room temperature for 2 h and refluxed for 30 min, then cooled to room temperature. Azidotrimethylsilane (0.77 g, 6.69 mmol) is added and the resulting solution is refluxed for 2 h. Tetrahydrofuran is removed under reduced pressure. Dry toluene (35 mL) is added, the solution is refluxed for 16 h and cooled to room temperature. The isocyanate **4a** thus formed is used without isolation. Toluene is removed under reduced pressure. 8% aqueous HCl (20 mL) and DME (10 mL) are added and the solution is stirred at room temperature for 16 h. The solvent is evaporated and the residue is partitioned between EtOAc and H_2O. The organic layer is dried ($MgSO_4$) and evaporated to give a white solid. This material is purified by column chromatography [EtOAc/petroleum ether (bp 30–60 °C), 1:4] to give **5a**; yield: 0.39 g (45%); mp 95–96 °C.

$C_{10}H_{13}NO_3$	calc.	C 61.53	H 6.71	N 7.18
(195.2)	found	61.55	6.69	7.12

Methyl 2-Ethoxycarbonylamino-4-methoxy-6-methylbenzoate (6a):

Isocyanate **4a** is generated as in the preceding procedure. Ethanol (2 mL) is added to the toluene solution of **4a** and the resulting solution is refluxed for 4 h. Work-up as above for **5a** gives a solid, which is further purified by column chromatography [EtOAc/petroleum ether (bp 30–60 °C), 1:10] to give **6a**; yield: 0.72 g (60%); mp 85–86 °C.

$C_{13}H_{17}NO_5$	calc.	C 58.42	H 6.44	N 5.24
(267.3)	found	58.55	6.43	5.24

Methyl 2-(3-Isopropylureido)-4-methoxy-6-methylbenzoate (7a):

Isocyanate **4a** is generated according to the procedure described for the preparation of **5a**. Isopropylamine (2 mL) is added to the toluene solution of **4a** and the resulting solution is stirred at room temperature for 2 h. Work-up as above for **5a** followed by column chromatography [EtOAc/petroleum ether (bp 30–60 °C), 1:5] gives **7a**; yield: 0.79 g (63%).

$C_{14}H_{20}N_2O_4$	calc.	C 59.99	H 7.19	N 9.99
(280.3)	found	59.95	7.23	9.93

2-Ethoxy-7-methoxy-5-methyl-4*H*-3,1-benzoxazin-4-one (8a):

A solution of the ester **6a** (100 mg, 0.374 mmol) in conc. H_2SO_4 (3 mL) is stirred at room temperature for 2 h, then added dropwise to an ice-cold stirred mixture of EtOAc (100 mL) and saturated $NaHCO_3$ solution (75 mL). The aqueous layer is further extracted with EtOAc (3 × 70 mL). The organic extract is dried ($MgSO_4$) and evaporated to give solid **8a**; yield: 60 mg (68%); mp 138–140 °C.

$C_{12}H_{13}NO_4$	calc.	C 61.27	H 5.57	N 5.95
(235.2)	found	61.40	5.63	5.87

2-Isopropylamino-7-methoxy-5-methyl-4*H*-3,1-benzoxazin-4-one (9a); Typical Procedure:

Following the procedure for the preparation of **8a**; the ester **7a** (401 mg, 1.43 mmol) is converted to **9a**, which is purified by thick-layer chromatography [EtOAc/petroleum ether (bp 30–60 °C); 1:5]; yield: 213 mg (60%); mp 138–140 °C.

$C_{13}H_{16}N_2O_3$	calc.	C 62.89	H 6.50	N 11.28
(248.2)	found	62.58	6.41	11.00

MS (70 eV): m/z = 248 (M^+), 206, 190, 164, 120.

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