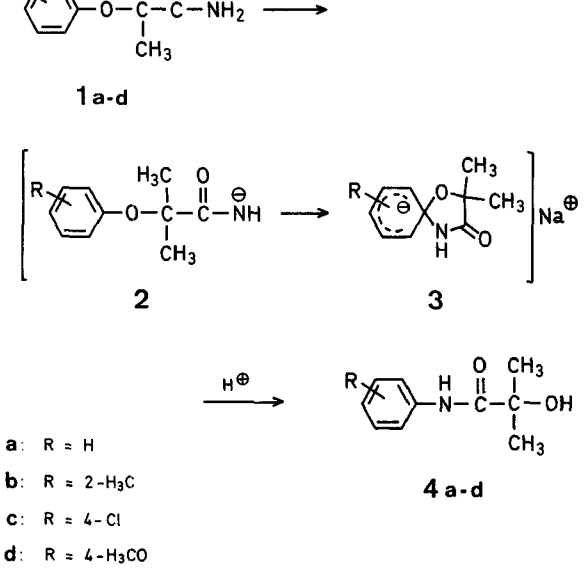
A Smiles Rearrangement Involving Non-Activated Aromatic Systems; the Facile Conversion of Phenols to Anilines

R. BAYLES, M. C. JOHNSON, R. F. MAISEY*, R. W. TURNER

Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England

In the preceding paper we described the Smiles rearrangement of 2-aryloxy-2-methylpropanamides to *N*-aryl-2-hydroxy-2-methylpropanamides. In all the examples cited the aromatic ring was activated to nucleophilic attack by an electron-withdrawing substituent. Smiles rearrangements[1,2] have generally involved highly activated aromatic ring systems, although there are a few exceptions[3,4]. Recently, activated or "naked" anions have found many applications in organic synthesis, including the facilitation of nucleophilic aromatic substitution[5].

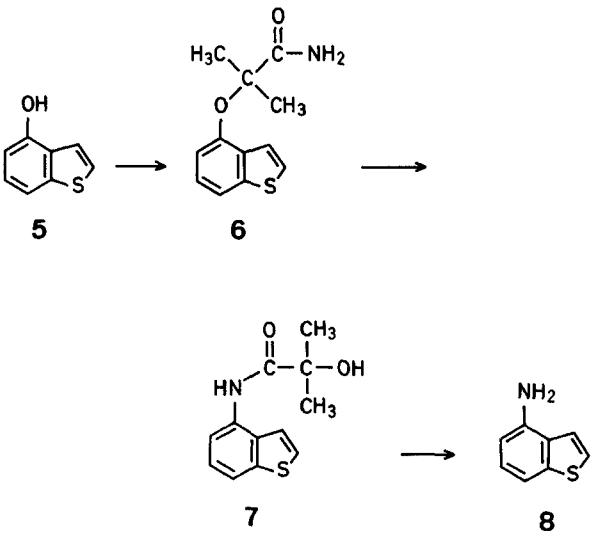
These anions are usually generated by using hexamethylphosphoric triamide as a solvent[6], or by means of crown ethers in acetonitrile[7]. This paper describes the use of hexamethylphosphoric triamide to extend the scope of the Smiles rearrangement to include 2-aryloxy-2-methylpropanamides which possess non-activated or deactivated benzene rings. This rearrangement now provides the basis of a new method for the conversion of phenols to anilines.



Sodium hydride in refluxing dioxan failed to produce rearrangement of the 2-methylpropanamides **1a–c**, which do not possess benzene rings activated to nucleophilic attack. However, treatment with sodium hydride in dimethylformamide at 100° for 16 h resulted in rearrangement to the *N*-aryl-2-hydroxy-2-methylpropanamides **4a–c**, respectively. When the reaction was carried out in hexamethylphosphoric triamide there was a dramatic increase in the reaction rate, the reaction being complete after 1 h at 100°, or after 16 h at ambient temperature. The results are summarised in Table 1. 2-(4-Methoxyphenoxy)-2-methylpropanamide (**1d**), in which the phenyl ring is deactivated, did not rearrange with sodium hydride in hexamethylphosphoric triamide at ambient temperature, but even this compound was rearranged after 16 h at 100°.

In contrast to these findings with 2-methylpropanamides, neither phenoxyacetamide nor 2-methylphenoxyacetamide was rearranged after prolonged treatment with sodium hydride in hexamethylphosphoric triamide at 100°. The important role of the α-methyl groups in facilitating this rearrangement was noted in the preceding paper[8]; in the case of the compounds described in this paper which possess non-activated or deactivated benzene rings, the α-methyl groups appear to be essential for the rearrangement to take place.

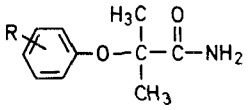
The *N*-aryl-2-hydroxy-2-methylpropanamides produced by this facile Smiles reaction are readily hydrolysed to the anilines in 70–85% yield (not optimised) by heating with 50% sulphuric acid or a mixture of 5 normal hydrochloric acid and dioxan. The 2-methyl-2-phenoxypropanamides **1** are readily synthesised[8] from the respective phenols in two stages and thus, this general rearrangement enables a phenol to be converted to an aniline in four stages under mild conditions. Only two general methods have hitherto been available to effect this conversion, one based on the thermal rearrangement of 4-aryloxy-2-phenylquinazolines[9], and the other utilising the rearrangement of aryl diethyl phosphates[10] by a mixture of potassium and potassium amide in liquid ammonia. Both of these methods, in contrast to the one reported here, involve rather drastic reaction conditions which limit their application. The new method is exemplified by the synthesis of 4-aminobenzothiophene (**8**) from 4-hydroxybenzothiophene (**5**); the yield at each stage was greater than 70% without optimisation.



Extensions of this novel reaction sequence to other phenols and heterocyclic systems are in progress.

2-Aryloxy-2-methylpropanamides (1); General Procedure:
These amides were synthesised from the corresponding 2-aryloxy-2-methylpropanoic acids[11] by the general procedure given in the preceding paper[8] (see Table 1).

Table 1. Preparation of 2-Aryloxy-2-methylpropanamides (**1**):

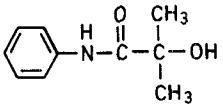


1	R	Yield [%]	m.p. (solvent)	Molecular formula[a]
a	H	70	110–111° (cyclohexane)	$C_{10}H_{13}NO_2$ (179.2)
b	4-Cl	75	120–122°	$C_{10}H_{12}ClNO_2$ (213.7)
c	2-H_3C	70	69–71°	$C_{11}H_{15}NO_2$ (193.2)
d	4-H_3CO	55	89–90° (cyclohexane)	$C_{11}H_{15}NO_3$ (209.2)

[a] All products gave satisfactory microanalyses (C ±0.2%, H ±0.2%, N ±0.1%).

***N*-Aryl-2-hydroxy-2-methylpropanamides 4; General Procedure:**
The 2-aryloxy-2-methylpropanamide (1.0 g) dissolved in either dry dimethylformamide or hexamethylphosphoric triamide (25 ml) was treated with 50% sodium hydride dispersion (1.1 mol-equiv) as detailed in Table 2. The resultant reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried and evaporated to give the product, which was then recrystallised.

Table 2. Preparation of *N*-Aryl-2-hydroxy-2-methylpropanamides 4



R	Solvent	Reaction conditions temp./time	Yield [%]	m.p. (solvent)	Molecular formula[a]
H	DMF	100°/16 h	80	131–133° (toluene)	$C_{10}H_{13}NO_2$ (179.2)
	HMPT	100°/1 h	85		
4-Cl	DMF	100°/16 h	80	135–136° (cyclohexane)	$C_{10}H_{12}ClNO_2$ (213.7)
	HMPT	25°/16 h	85		
2-H_3C	DMF	100°/16 h	45	83–85° (cyclohexane)	$C_{11}H_{15}NO_2$ (193.2)
	HMPT	100°/1 h	60		
4-H_3CO	HMPT	100°/16 h	50	136–138° (cyclohexane)	$C_{11}H_{15}NO_3$ (209.2)

[a] All products gave satisfactory microanalyses (C ±0.3%, H ±0.2%, N ±0.1%).

Hydrolysis of *N*-(4-Nitrophenyl)-2-hydroxy-2-methylpropanamide:
The anilide (300 mg) was heated with 5 normal hydrochloric acid (5 ml) and dioxan (5 ml) for 2 h on a steam bath. The reaction mixture was made alkaline and extracted with ethyl acetate. The extract was evaporated and the residue crystallised from water to give 4-nitroaniline; yield: 180 mg (70%); m.p. 148°.

2-(Benzo[*b*]thiophen-4-yloxy)-2-methylpropanoic Acid:
4-Hydroxybenzo[*b*]thiophene[12] was subjected to the general method of preparation of 2-aryloxy-2-methylpropanoic acids described in the preceding paper[8] to give the acid; yield: 75%; m.p. 127° (petroleum ether b.p. 60–80°).

$C_{12}H_{12}O_3S$ (236.3)	calc.	C 60.9	H 5.1	S 13.6
	found	61.0	5.1	13.2

2-(Benzo[*b*]thien-4-yloxy)-2-methylpropanamide (60):
A mixture of oxalyl chloride (7 ml) and dimethylformamide (1 ml) was added dropwise over a period of thirty minutes to a solution of 2-(benzo[*b*]thiophen-4-yloxy)-2-methylpropanoic acid (7.0 g) in toluene (100 ml). The reaction mixture was evaporated and the residue dissolved in dioxan (100 ml). Ammonia solution (d = 0.880, 100 ml) was added slowly. When the addition was complete the reaction mixture was stirred at room temperature for one hour then evaporated to half volume and partitioned between ethyl acetate and water. The organic phase was washed with normal sodium hydroxide solution and with water and then evaporated. Crystallisation of the residue from cyclohexane furnished the 2-methylpropanamide; yield: 4.9 g (70%); m.p. 127–129°.

$C_{12}H_{13}NO_2S$ (235.3)	calc.	C 61.2	H 5.5	N 6.0 S 13.6
	found	61.1	5.5	5.9 13.2

***N*-Benzo[*b*]thien-4-yl-2-hydroxy-2-methylpropanamide (7):**
Sodium hydride dispersion (80%, 0.20 g) was added carefully to a solution of the amide **6** (1.0 g) in dry hexamethylphosphoric triamide (3 ml). The reaction mixture was heated on a steam bath for one hour, diluted with water, and extracted with ethyl acetate. The extract was evaporated and the residue crystallised from toluene to give the product; yield: 0.72 g (72%); m.p. 142–143°.

$C_{12}H_{13}NO_2S$ (235.3)	calc.	C 61.2	H 5.5	N 6.0 S 13.6
	found	61.2	5.7	5.8 13.2

4-Aminobenzo[*b*]thiophene (8):
The amide **7** (9.1 g) was heated at 100° with 50% sulphuric acid (100 ml) for two hours. The resultant solution was cooled, made alkaline with 5 normal sodium hydroxide solution and extracted with ether. The ether was evaporated to give the amine which was crystallised from hexane; yield: 3.5 g (70%); m.p. 50° (Lit.[13] m.p. 50–51°).

Received: August 23, 1976

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