COMMUNICATIONS

The Smiles Rearrangement of 2-Aryloxy-2-methylpropanamides. Synthesis of *N*-Aryl-2-hydroxy-2-methylpropanamides

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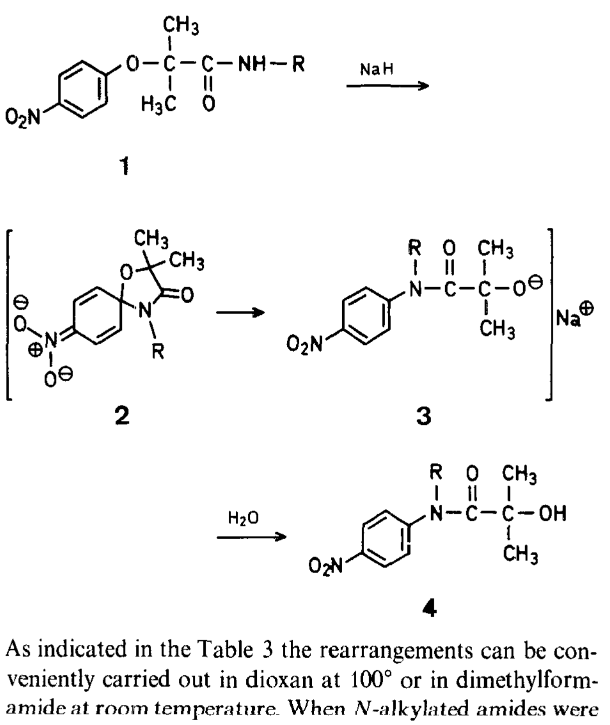
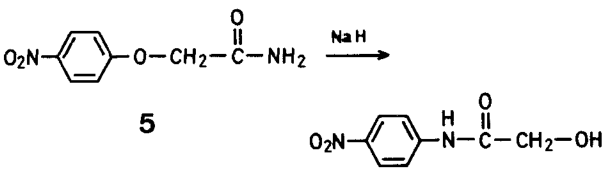
N-Aryl-2-hydroxy-2-methylpropanamides have been recently shown to possess antiandrogenic properties in animals[1]. In this paper we wish to describe the synthesis of these compounds by the facile Smiles rearrangement of 2-aryloxy-2-methylpropanamides. Treatment of 2-methyl-2-(4-nitrophenyl)-propanamide (**1**, R = H) with sodium hydride in refluxing dioxan furnished *N*-(4-nitrophenyl)-2-hydroxy-2-methylpropanamide (**4**, R = H). The reaction was carried out with other ring activated aryloxyisobutyramides and the results are shown in Table 3. The products obtained were identical to anilides synthesised conventionally from the respective anilines[1].

By analogy with the addition-elimination mechanism proposed for the Smiles[2,3] rearrangement, the formation of (**4**, R = H) must involve nucleophilic attack of the amide anion to give the spiro-intermediate (**2**, R = H) followed by the breakdown of **2** (R = H) and protonation of **3** to give the anilide **4** (R = H). In contrast to the normal Smiles rearrangement, in this reaction the carbon bridge between the hetero-atoms is acyclic and not part of an aromatic ring. A growing number of examples of this type of rearrangement has been reported in recent years[4-7].



As indicated in the Table 3 the rearrangements can be conveniently carried out in dioxan at 100° or in dimethylformamide at room temperature. When *N*-alkylated amides were utilised such as the secondary amide **1** (R = CH_3) the reaction proceeded at a much slower rate, refluxing for 140 h in dioxan with excess sodium hydride producing only a 25% conversion to the anilide **4** (R = CH_3).



A similar reaction retardation occurred when the α-methyl groups were replaced by hydrogen atoms, 2-(4-nitrophenoxy)-ethanamide (**5**) was unaffected when refluxed with sodium hydride in dioxan. However, reaction in dimethylformamide at 50° produced the Smiles rearrangement product **6**. It would seem that the spiro-transition state is more readily formed when the two α-methyl groups are present. A similar observation has been reported by Corey[8], who noted that the 2-methyl-2-phenoxypropanoic acid (**7**, R = CH_3) was converted by bromine in alkaline solution in excellent yield to the spiro-cyclohexadiene **8** (R = CH_3), whereas the phenoxyacetic acid (**7**, R = H) only gave poor yields of **8** (R = H). The analogy is not a perfect one, since in the cyclohexadiene examples the situation is complicated by the possibility of *ortho*-ring and active methylene bromination.

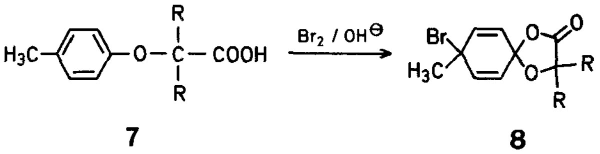
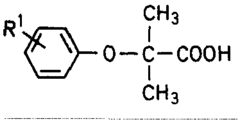


Table 1. Preparation of 2-Aryloxy-2-methylpropanoic Acids

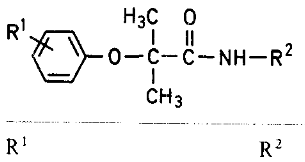


R^1	Yield [%]	m.p. (solvent)	Molecular formula[a] or Lit. m.p.
4-O_2N	45	121-123° (water)	Lit.[9] 123°
3-F_3C, 4-O_2N	–	oil[b]	–
4-C_6H_5—CO—	75	128-131° (ethyl acetate/ petr. ether)	$C_{17}H_{16}O_4$ (284.3)
2-C_6H_5—CO, 4-Cl	65	138-140° (cyclohexane)	$C_{17}H_{15}ClO_4$ (318.8)

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

[b] Recrystallised ethyl acetate/petroleum ether.

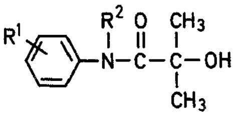
Table 2. Preparation of 2-Aryloxy-2-methylpropanamides **1**



R^1	R^2	Yield [%]	m.p. (solvent)	Molecular formula[a]
4-O_2N	H	60	158-160° (benzene/petroleum ether)	$C_{10}H_{12}N_2O_4$ (224.2)
4-O_2N	CH_3	70	92-93° (benzene/petroleum ether)	$C_{11}H_{14}N_2O_4$ (238.2)
3-F_3C, 4-O_2N	H	65	133-135° (toluene)	$C_{11}H_{11}F_3N_2O_4$ (281.1)
4-C_6H_5—CO	H	75	143-145° (ethyl acetate)	$C_{17}H_{17}NO_3$ (283.3)
2-C_6H_5—CO, 4-Cl	H	80	114-115° (benzene/petroleum ether)	$C_{17}H_{16}ClNO_3$ (317.7)

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

Table 3. Preparation of *N*-Aryl-2-hydroxy-2-methylpropanamides **4**



R^1	R^2	Amount of NaH (equiv)	Solvent	Reaction conditions temp./time	Yield[a] [%]	m.p. (solvent)	Molecular[b] formula
4-O_2N	H	1.1	dioxan	100°/6 h	75	178-180° (ethanol)	$C_{10}H_{12}N_2O_4$ (224.2)
3-F_3C, 4-O_2N	H	3.0	DMF	25°/10 min	60	149-151°[c] (toluene)	–
2-C_6H_5—CO, 4-Cl	H	1.0	DMF	25°/3 h	65	128-130° (cyclohexane)	$C_{17}H_{16}ClNO_3$ (317.7)
		1.0	dioxan	100°/16 h	50		
4-C_6H_5—CO—	H	4.0	DMF	25°/2 h	65	134-135° (toluene)	$C_{17}H_{17}NO_3$ (283.3)
4-O_2N	CH_3	2.0	dioxan	100°/140 h	25	128-129° (toluene)	$C_{11}H_{14}N_2O_4$ (238.2)

[a] Yields were not optimised.

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

[c] Lit.[1] m.p. 152°.

An examination of the reaction of a variety of α-alkylated *p*-nitrophenoxyacetamides with bases, is being undertaken to determine the optimum α-substituents for a facile Smiles rearrangement.

2-Aryloxy-2-methylpropanoic Acids; General Procedure:

Ground sodium hydroxide flake (3.3 mol) was added slowly to a solution of the corresponding phenol (0.5 mol) dissolved in acetone (600 ml), keeping the temperature below 35°. When the addition was complete, the mixture was refluxed gently and chloroform (0.75 mol) was added at a rate to maintain boiling. After the chloroform addition the mixture was refluxed for 4 h. The acetone was evaporated and the residue dissolved in water (500 ml) and acidified. An ether extract, on evaporation and recrystallisation furnished the 2-aryloxy-2-methylpropanoic acid (see Table 1).

2-Aryloxy-2-methylpropanamides; General Procedure:

2-Aryloxy-2-methylpropanoic acid (3.0 g) was refluxed with thionyl chloride (15 ml) for 1 h. The thionyl chloride was evaporated and the crude acid chloride dissolved in dioxan and cooled. A solution of excess ammonia or amine in dioxan was added and the mixture stirred for 5 h at room temperature. The dioxan was removed under vacuo and the residue recrystallised to give the required propanamide (see Table 2).

***N*-Aryl-2-hydroxy-2-methylpropanamides; General Procedure:**

The 2-aryloxy-2-methylpropanamide (1.0 g) in either dry dimethylformamide or dioxan (10 ml) solution is treated with 50% sodium hydride dispersion as detailed in Table 3. Removal of the solvent and partition between ethyl acetate and water followed by evaporation of the organic phase gave the crude anilide, which was then recrystallised.

2-Hydroxy-4-nitroacetanilide (5):

A solution of 4-nitrophenoxyacetamide (2.7 g) in dry dimethylformamide (20 ml) was treated with 50% sodium hydride dispersion (0.73 g) and the mixture stirred at 50° for 1 h. Water was added and the resulting precipitate was filtered and recrystallised from ethyl acetate to give the anilide; yield: 1.2 g (45%); yellow prisms; m.p. 194°.

$C_8H_8N_2O_4$	calc.	C 49.0	H 4.1	N 14.2
(196.2)	found	49.0	4.1	13.9

I.R. (nujol mull): ν_{max} = 1670 (C=O), 3320 (OH), 3400 (NH) cm^{-1}.

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