

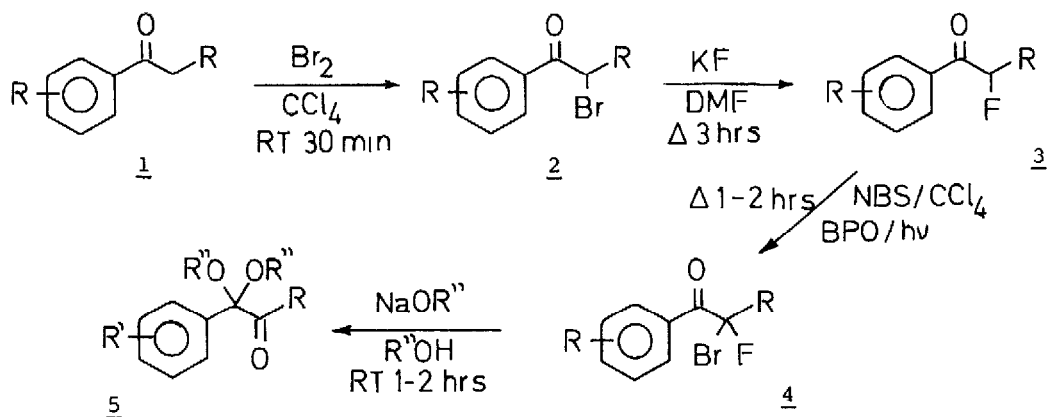
REGIOSPECIFIC SYNTHESIS OF  $\alpha$ -KETOACETALS BY REARRANGEMENT OF  $\alpha$ -BROMO-  
 $\alpha$ -FLUOROKETONES

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**Abstract** :  $\alpha$ -Ketoacetals, derived from alkylaryl- $\alpha$ -diones and with acetalized benzoyl moiety, were synthesized by alkoxide induced rearrangement of  $\alpha$ -bromo- $\alpha$ -fluoroalkylarylketones.

Protection of the carbonyl group as an acetal is a frequently encountered process in preparative organic chemistry, especially when multi-step syntheses are involved. Selective monoacetalization of unsymmetrical  $\alpha$ -diones may be of considerable value. Several methods exist for the synthesis of  $\alpha$ -ketoacetals, among others direct acetalization of  $\alpha$ -diones,<sup>2</sup> reaction of organometallic reagents on  $\alpha,\alpha$ -dialkoxy-esters<sup>3</sup> or -amides,<sup>4</sup> oxidation of  $\alpha$ -sulfonylated ketones with methanolic thallium (III)nitrate<sup>5</sup> or oxidation of  $\alpha$ -hydroxyacetals.<sup>6</sup> Additionally,  $\alpha$ -ketoacetals were synthesized via dichloromethylketimines,<sup>7</sup> rearrangement of  $\alpha,\alpha$ -dihaloketones,<sup>8</sup> via  $\alpha$ -acetoxy- $\alpha$ -sulfonylated ketones,<sup>9</sup> or through metallation of imino derivatives of pyruvic aldehyde dimethyl acetal.<sup>10</sup>

Connected with our studies in the field of the rearrangements of  $\alpha,\alpha$ -dihaloalkylarylketones,<sup>8</sup> we required a synthesis of 1,1-dialkoxy-1-aryl-2-alkanones 5. Acetalization of alkylaryl- $\alpha$ -diones (HCl/CH<sub>3</sub>OH) is not applicable in this case since the more reactive acyl moiety is initially acetalized, but the product rapidly isomerizes to its isomeric  $\alpha$ -ketoacetal under the acidic reaction conditions used, finally resulting in a mixture of both  $\alpha$ -ketoacetals. While  $\alpha,\alpha$ -dichloroalkylarylketones underwent an alkoxide-induced rearrangement into isomeric  $\alpha,\alpha$ -dialkoxyketones,<sup>8</sup> the reaction of  $\alpha$ -bromo- $\alpha$ -fluoroalkylarylketones 4 with alkoxides in alcoholic medium exclusively produced 1,1-dialkoxy-1-aryl-2-alkanones 5.



The starting materials 4 were synthesized from alkylarylketones 1 via  $\alpha$ -bromo-ketones 2 and  $\alpha$ -fluoroketones 3. The latter were prepared by halide exchange with dry potassium fluoride in dimethylformamide. Several methods exist for the synthesis of  $\alpha$ -fluoroketones<sup>11</sup> but our procedure using KF/DMF reagent seemed a valuable reaction as isolated yields (distillation) varied from 60 to 75 %. The bromination of  $\alpha$ -fluoroketones 3 into 4 was affected by NBS/BPO/CCl<sub>4</sub> under UV-irradiation and isolated yields (distillation) of 72-86 % were obtained. The rearrangement of  $\alpha$ -bromo- $\alpha$ -fluoroketones 4 with sodium alkoxides (1N; 3 equivalents; RT 1-2 hrs) gave  $\alpha$ -ketoacetals 5 as the sole products but substantial losses due to decomposition were noticed during distillation. The results of the synthesis of  $\alpha$ -ketoacetals 5 are compiled in the Table.

The four-step-sequence starting from alkylarylketones 1 and leading to  $\alpha,\alpha$ -dialkoxy- $\alpha$ -arylketones 5 represents an elegant route to regiospecifically acetalized  $\alpha$ -diones. It is not necessary to isolate intermediate compounds 2, 3 or 4. As an example, starting from propiophenone (0.2 mole scale) there was obtained a 62 % overall yield of 1,1-diethoxy-1-phenyl-2-propanone 5b (R=Me; R'<sup>1</sup>=H; R''=Et).

Similar to the rearrangement of  $\alpha,\alpha$ -dihaloaldehydes<sup>12</sup> and  $\alpha,\alpha$ -dichloroalkylarylketones,<sup>8</sup> the mechanism proceeds via the intermediacy of  $\alpha$ -fluoro- $\alpha'$ -alkoxyepoxides 6 formed by nucleophilic attack of the alkoxide anion at the carbonyl group of 4 and subsequent intramolecular bromide anion displacement. The highly reactive  $\alpha$ -fluoroepoxides 6 rearranged spontaneously to 1-alkoxy-1-aryl-1-fluoro-2-alkanones 7, a phenomenon which is well-known in the  $\alpha$ -haloepoxide

TABLE . Synthesis of 1,1-Dialkoxy-1-aryl-2-alkanones 5<sup>a</sup>

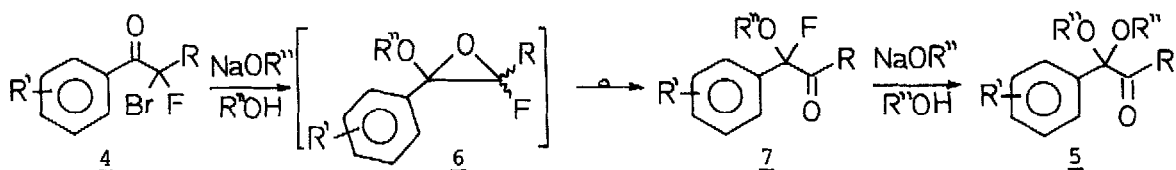
|           | R            | R'           | R''          | b.p.               | yield <sup>b</sup> |
|-----------|--------------|--------------|--------------|--------------------|--------------------|
| <u>5a</u> | Me           | H            | Me           | 123-125°/11 mmHg   | 75 %               |
| <u>5b</u> | Me           | H            | Et           | 124-132°/16 mmHg   | 69 %               |
| <u>5b</u> | Me           | H            | Et           | 78- 83°/0.01 mmHg  | 62 % <sup>c</sup>  |
| <u>5c</u> | Me           | H            | <u>n</u> -Pr | 80- 81°/0.1 mmHg   | 71 %               |
| <u>5d</u> | Me           | H            | <u>1</u> -Pr | 75- 80°/0.15 mmHg  | 70 %               |
| <u>5e</u> | Me           | <u>m</u> -Br | Et           | 105-111°/0.01 mmHg | 57 %               |
| <u>5f</u> | Me           | <u>m</u> -Br | <u>n</u> -Pr | 141-144°/0.01 mmHg | 51 %               |
| <u>5g</u> | Et           | H            | Me           | 73- 80°/0.2 mmHg   | 70 %               |
| <u>5h</u> | Et           | H            | Et           | 80- 84°/0.1 mmHg   | 72 %               |
| <u>5i</u> | <u>n</u> -Pr | H            | Me           | 78- 80°/0.5 mmHg   | 76 %               |

a Compounds 5 gave satisfactory combustion data and were fully characterized by NMR, IR and MS data.

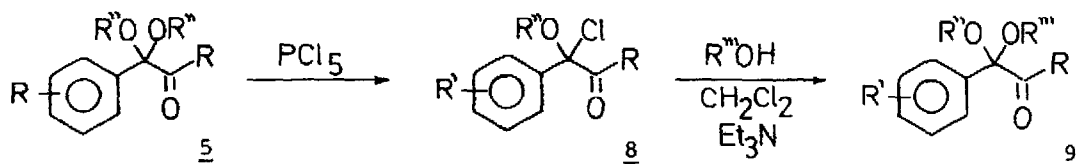
b Isolated yields obtained starting from  $\alpha$ -bromo- $\alpha$ -fluoroketones 4, except otherwise stated.

c Yield starting from propiophenone according to the four-step sequence, without isolation of any intermediate.

chemistry.<sup>13</sup> Finally, the transient  $\alpha$ -alkoxy- $\alpha$ -fluoroketones 7 were converted exclusively into the title compounds 5 by the alkoxide. In the case of  $\alpha,\alpha$ -di-



chloroalkylarylketones, the reaction proceeded in similar way to an  $\alpha$ -alkoxy- $\alpha$ -chloroketone (analogous to 7), but the latter intermediate suffered also carbonyl addition and subsequent epoxide formation, thereby generating two isomeric  $\alpha$ -ketoacetals. We are currently investigating in more detail the reactive behavior of  $\alpha,\alpha$ -dihaloalkylarylketones towards alkoxides. In particular, the influence of various reaction conditions on the reaction pathways is studied and will be reported in a forthcoming paper.  $\alpha$ -Ketoacetals 5 can also be used as substrates for the synthesis of mixed acetals. The procedure involves conversion of 5 into  $\alpha$ -alkoxy- $\alpha$ -chloroketone 8 with phosphorus pentachloride and subsequent treatment of 8 with an alcohol in dichloromethane in the presence of triethylamine. As an example, 1,1-diethoxy-1-phenyl-2-propanone 5b was converted



into 1-ethoxy-1-isopropoxy-2-propanone 9 (R=Me; R'=H; R''=Et; R''' = 1-Pr) in 72 % yield (b.p. 65-68°/0.01 mmHg).

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