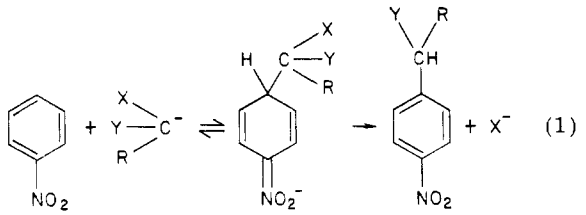
Communications

On the Mechanism of the Vicarious Nucleophilic Substitution of Hydrogen in Nitroarenes[1]

Summary: On the basis of the isotope effect and the effect of base on the reaction rate the main features of the mechanism of the vicarious nucleophilic substitution of hydrogen were established. The reaction proceeds via fast and reversible addition of the carbanions to the nitroarenes followed by slower base-induced β-elimination.

Sir: The vicarious nucleophilic substitution of hydrogen defined as a reaction between carbanions containing leaving groups at the carbanionic centers and nitroarenes resulting in the replacement of a hydrogen atom ortho or para to the nitro group with the carbanion moiety proceeds according to eq 1:



(1)

with X = leaving group, Y = carbanion stabilizing group, and R = substituent.

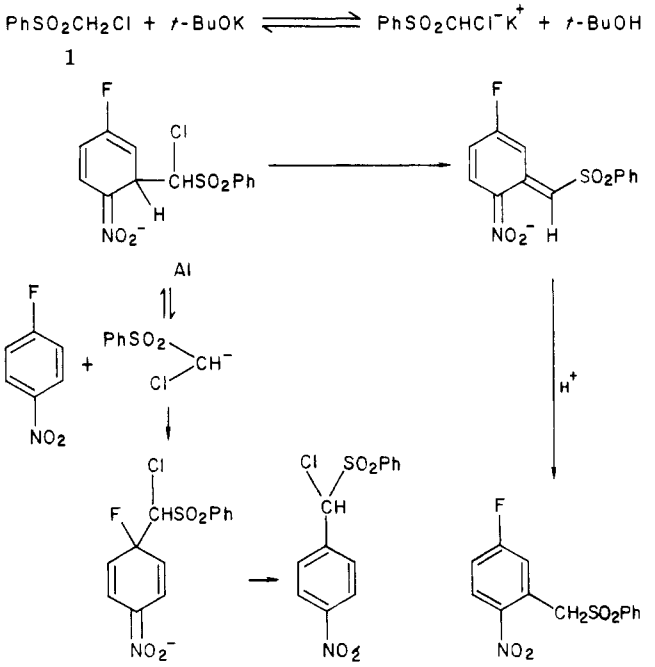
The process is of general character concerning the type of the carbanion (X = Cl, Br, OPh, SPh, etc.; Y = SO_2Ph, SOPh, CN, COOR, etc.; R = H, alkyl, aryl, etc.) and nitroarenes and offers a simple access to a variety of substituted nitroarenes.[2-4]

In designing the reaction we were looking for a way to remove the hydride anion from σ complex A, and our concept was that the leaving group will depart from this intermediate complex with simultaneous hydride shift to form the product.[2] Although the process indeed occurs according to the anticipated stoichiometry, it does not mean that this mechanistic scheme is necessarily correct. Among other mechanistic possibilities of the transformation of the complex, the most feasible seems to be base-induced β-elimination E2 or E1cB. Another important question here is the reversibility of the σ complex formation.

Here we would like to present the general mechanistic picture of this reaction based on preliminary experimental data: the determination of the kinetic isotope effect and the influence of base on the reaction rate.

In the reaction of nitrobenzene-*4-d*[5] with chloromethyl phenyl sulfone (1), the secondary kinetic isotope effect was found $k_H/k_D = 0.90 \pm 0.04$ on the basis of the differences in the ratio of the ortho and para substitution in nitrobenzene and nitrobenzene-*4-d*. The ratios of ortho to para isomers in nitrobenzene and nitrobenzene-*4-d* were 1.59 and 1.43, respectively.[6]

Scheme I[a,b]



	t-BuOK/1 ratio	yield, % 2	3
1	1.0	12	14
2	2.0	8	66
3	4.0	trace	58
4[b]	2.0	49	11

[a] To a solution of 1 (0.48 g, 2.5 mmol) in dry Me_2SO (18 mL) was added commercial *t*-BuOK (0.30, 0.60, or 1.20 g), after 2 min of vigorous stirring at 20 °C, 4-fluoronitrobenzene (0.35 g, 2.5 mmol) in Me_2SO (2 mL) was added in one portion. The reaction mixture was kept at 20 to 22 °C for 10 min and quenched with dilute HCl. The products were extracted with CH_2Cl_2, and yields were determined by GLC analysis. [b] Entry 4: to a solution of the nitroarene and 1 was slowly added a solution of *t*-BuOK in Me_2SO dropwise.

The base effect on the rate of the substitution of hydrogen was studied by using intramolecular competition with the substitution of fluorine. It was already observed[4,7] that the reaction of 1 with 4-fluoronitrobenzene carried

(1) Part 108 in the series Reactions of Organic Anions, part 107: Goliński, J.; Mąkosza, M.; Rykowski, A. *Tetrahedron Lett.* **1983**, *24*, 3279.
(2) Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, 3495.
(3) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1980**, *45*, 1534. Mąkosza, M.; Goliński, J. *Angew. Chem.* **1982**, *94*, 468. Mąkosza, M.; Goliński, J.; Pankowski, J. *Synthesis* **1983**, 40.
(4) Mąkosza, M. In "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: New York, 1983; p 401.
(5) Nitrobenzene-*4-d* of 94% isotopic purity was obtained by a modified procedure (Hoeg, J. H. *J. Labelled. Compd.* **1971**, *7*, 179) in the following manner: to dry 4-nitrobenzenediazonium tetrafluoroborate (5 g) suspended in D_2O (100 mL) was added deuterated hypophosphorous acid (8 g). The mixture was vigorously stirred at room temperature for 30 min, and the product was extracted with CCl_4. Nitrobenzene-*4-d* was purified by column chromatography on silica gel, yield 71%.
(6) Usually KOH or NaOH in Me_2SO is used as convenient base solvent systems for the vicarious substitution of hydrogen.[2,3] For the mechanistic studies it was necessary to use a homogeneous solution of *t*-BuOK in Me_2SO. The reactions were carried out as follows: 1 (0.5 mmol) in Me_2SO (7 mL) was treated with a solution of *t*-BuOK in Me_2SO (2 mL 0.5 M), and after 1 min nitrobenzene or nitrobenzene-*4-d* (0.5 mmol) in Me_2SO (1 mL) was added. After 1 min, the reaction was quenched with dilute HCl. The products were extracted with CH_2Cl_2 and the ortho/para ratios were determined by GLC analysis. Total yields determined with internal standard were about 75%.
(7) Goliński, J. Ph.D. Dissertation, Technical University, Warsaw, 1979.

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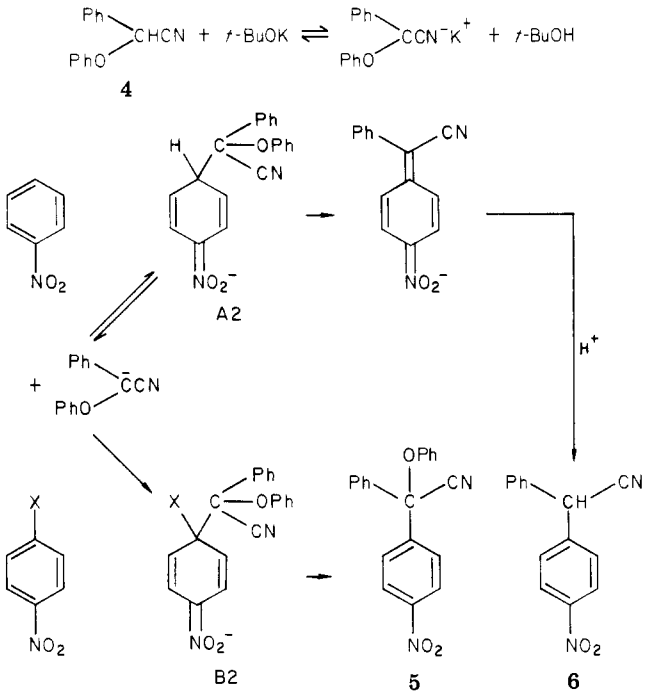
Scheme II[a]



	X	t-BuOK/4 ratio	yield, % 5	6
1	F	1.0	54	10
2	F	2.0	36	30
3	F	4.0	trace	50
4	Cl	1.0	56	8
5	Cl	2.0	24	45

[a] Tertiary carbanions replace hydrogen only para to the nitro group.[4] The procedure was identical to that applied for the reaction between 1 and 4-fluoronitrobenzene. Yields were determined after separation of the products by column chromatography.

out in the presence of an excess of NaOH in Me_2SO results in the substitution of both hydrogen and fluorine. Therefore, this reaction was used for studies of the competition.

The rates of the formation of σ complexes A1 and B1 and the conversion B1 → **2** do not depend on the presence of excessive base. On the other hand, the transformation of A1 into **3** should be accelerated if it proceeds via β-elimination and should not be if it involves the hydride shift. Hence, if the vicarious substitution of hydrogen proceeds via the hydride shift, the product ratio **2**/**3** should not be influenced by an excessive base; on the contrary, if it proceeds via β-elimination, an excess of base should favor the formation of **3**. The results shown in Scheme I lead to the conclusion that the reaction proceeds via β-elimination.

The same conclusion could be derived from the intermolecular competition of the substitution of hydrogen and halogen in nitrobenzene and 4-halonitrobenzene with tertiary carbanion of phenoxyphenylacetonitrile (**4**). (Scheme II). Here the tendency for substitution of halogen is more pronounced than in the case in Scheme I, but when the base concentration is high enough the substitution of hydrogen in nitrobenzene occurs exclusively.

The results shown in Schemes I and II allow one to exclude the hydride shift and accept the β-elimination as the way of transformation of σ complexes A into the products of the vicarious substitution. So far the differentiation between E2 and E1cB eliminations cannot be perceived.

The results shown in Schemes I and II evidence also reversibility of the formation of σ complexes A. Indeed, taking into account that the rate of the replacement of halogen by carbanions is not influenced by bases, the fact that an excess of base, via acceleration of the conversion of σ complexes A1 and A2 changes the reaction course shows that these complexes are formed in fast and reversible process.

The same conclusion can be drawn from the value of the isotope effect. Since the formation of σ complex A is not the rate-limiting step, the isotope effect is thermodynamic in its nature—the presence of deuterium instead of hydrogen atom shifts the equilibrium to the side of the σ complex, and, in consequence, deuterium is substituted somewhat faster than hydrogen. The absence of the primary isotope effect is, in our opinion, due to the nonsymmetric transition state of the β-elimination step.

The detailed results of further studies on the mechanism of this reaction will be published later.

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Registry No. **1**, 7205-98-3; 1 anion, 87013-25-0; **4**, 32121-27-0; **4** anion, 87013-26-1; D, 7782-39-0; nitrobenzene, 98-95-3; 4-fluoronitrobenzene, 350-46-9; 4-chloronitrobenzene, 100-00-5; 4-nitrobenzenediazonium tetrafluoroborate, 456-27-9; nitrobenzene-*4-d*, 13122-36-6.

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Total Syntheses of (±)-Mesembrine, (±)-Joubertinamine, and (±)-*N*-Demethylmesembrenone

Summary: The syntheses of three members of the sceletium alkaloid family are developed from a common synthon, leading to short, high-yielding stereorational routes to (±)-mesembrine, (±)-joubertinamine, and (±)-*N*-demethylmesembrenone. The latter is synthesized for the first time and allows its previously postulated role in providing the complex racemic alkaloid channaine to be examined. The sequence of reactions employed in obtaining the above alkaloids represents new synthetic methodology that is likely to be generally useful in providing an efficient entry into complex molecules containing a cis-2,3-fused pyrrolidine nucleus.

Sir: We have described recently a general synthetic route to the octahydroindole alkaloids of the mesembrine family and related bases of the joubertiamine type.[1] This synthesis had as its cornerstone the formation of a cis bicyclo[4.2.0]octanone and a controlled unidirectional aza-ring expansion of the latter to the octahydroindolone nucleus. Herein is described an alternative approach that has improved flexibility over the modified Beckman rearrangement utilized previously.

Besides the demonstration of efficient synthetic methodology, there is other motivation to prepare (±)-*N*-demethylmesembrenone. In pursuing isolation and structural studies of alkaloids of the *Sceletium* family, characteri-

(1) Jeffs, P. W.; Cortese, N.A.; Wolfram, J. *J. Org. Chem.* **1972**, *47*, 3881.

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