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The Vicarious Nucleophilic Substitution of Hydrogen Proceeding *via* a Cyclopropane Ring-Opening

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Abstract: 1-Cyano-2,2-diethoxycarbonyl cyclopropane was reacted with several nitroarenes under basic conditions. The reaction proceeded according to the vicarious nucleophilic substitution of hydrogen scheme; i.e. the initially formed σ-adducts underwent base-induced elimination, resulting in cleavage of the cyclopropane ring. The *ortho*-substituted products can be directly transformed into substituted *N*-hydroxyindoles.

Keywords: cyclopropanes; carbanions; nitro compounds, substitution.

Electrophilic cyclopropanes easily undergo reactions with nucleophiles resulting in opening of the three-membered ring [1]. This reaction has been widely used in organic synthesis [2]. The ring-opening reaction can also be triggered by nucleophilic attack on some other site of a molecule containing the cyclopropane moiety [3] or by formation of a carbanionic center on a carbon atom adjacent to the ring [4]. In those cases eliminative ring cleavage takes place and the carbon atom bearing two electron-withdrawing substituents acts as a leaving group. The concept of stabilizing an unstable intermediate *via* a cyclopropane ring-opening led us to the idea of a reaction consisting of addition of a cyclopropane anion, represented by a general structure **1** (Scheme 1), to an electrophilic molecule followed by transformation of the adduct to a stable product *via* a three-membered ring cleavage. Thus the usual reactivity of an electrophilic cyclopropane would be taken advantage of only in the second step, whereas in the first step a cyclopropyl moiety would act as a *nucleophile*, to form a carbon-carbon bond. Three possible electrophilic components for the reaction were considered (Scheme 1): an aldehyde, an electrophilic olefin and an aromatic nitro compound which would give the Darzen's (eq. 1), cyclopropanation (eq. 2) and the vicarious nucleophilic substitution of hydrogen (VNS) [5] (eq. 3) reactions, respectively. The latter possibility appeared particularly promising as upon formation of the adduct, such as **2**, the tendency for formation of a highly conjugated anion provides a powerful

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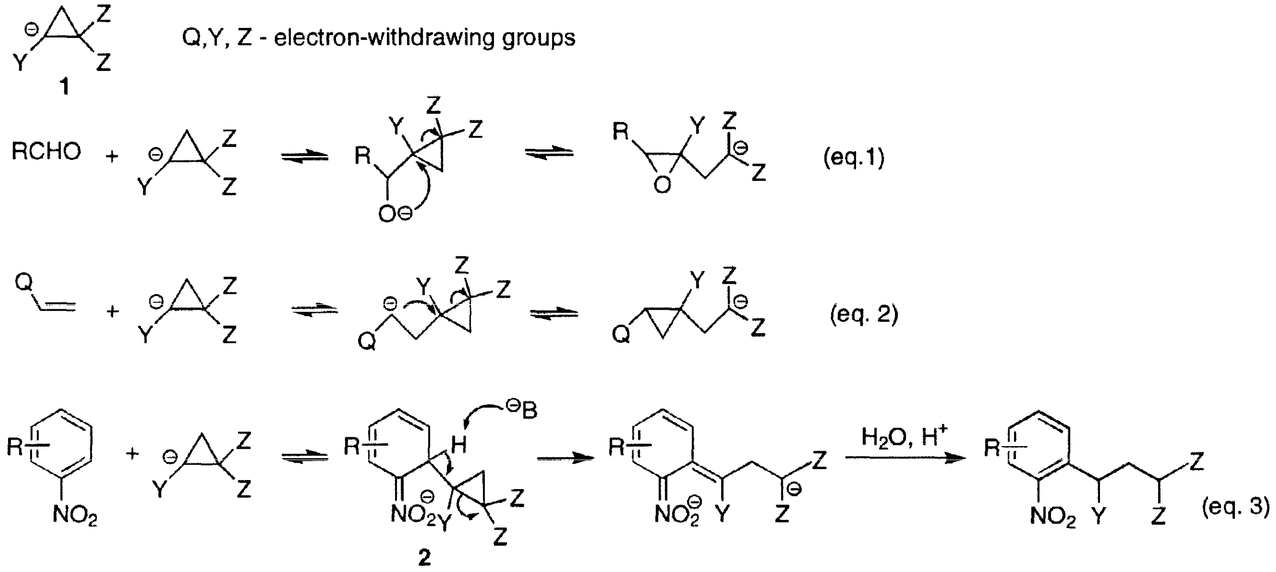
driving force for the subsequent irreversible elimination, whereas in the two former cases all steps could be reversible. Also somewhat similar VNS reaction with an oxirane has been reported [6].



Scheme 1

Another important issue was a choice of the carbanion-stabilizing group Y. Cyclopropyl carbanions are known to be more difficult to generate as compared to their open chain analogs and once formed - extremely reactive and prone to self-condensation and cyclopropyl-allyl anion isomerization [7]. The extent of these reactions depends heavily on the nature of the negative charge-stabilizing group. In some cases (EWG=NO_2, CHO, COOR, CO_2^-) the reaction of cyclopropyl carbanions with electrophiles is difficult or impossible to execute.[2] In other cases (EWG=SO_2Ph, CN, NC, $^+PPh_3$, $^+SPh_2$) reasonably good results have been reported [7]. In view of the published data the cyano substituent appeared to be promising.

Thus 1-cyano-2,2-diethoxycarbonyl cyclopropane **3** was chosen as a model compound, prepared according to a published procedure [8] and subjected to reaction with several aromatic nitro compounds under typical VNS reaction conditions.[3] Indeed, the foreseen reaction took place (Scheme 2) and the results are summarized in Table 1. The expected products **4a-4d**, **6d** were accompanied by mono-transesterification products **5a-7d**, **7d**, which were isolated as 1:1 mixtures of diastereoisomers. In the *para*-substituted nitrobenzenes the reaction proceeded in the position *ortho* to the nitro group. No substitution of the chlorine atom took place in the case of *p*-chloronitrobenzene, once again proving the general rule that the VNS of hydrogen proceeds faster than the conventional S_NAr of a halogen [5a]. Also *o*-chloronitrobenzene entered the reaction with **3**, but an attempt to separate the resulting mixture failed and the ^1H NMR analysis of the partially resolved products did not allow their unambiguous

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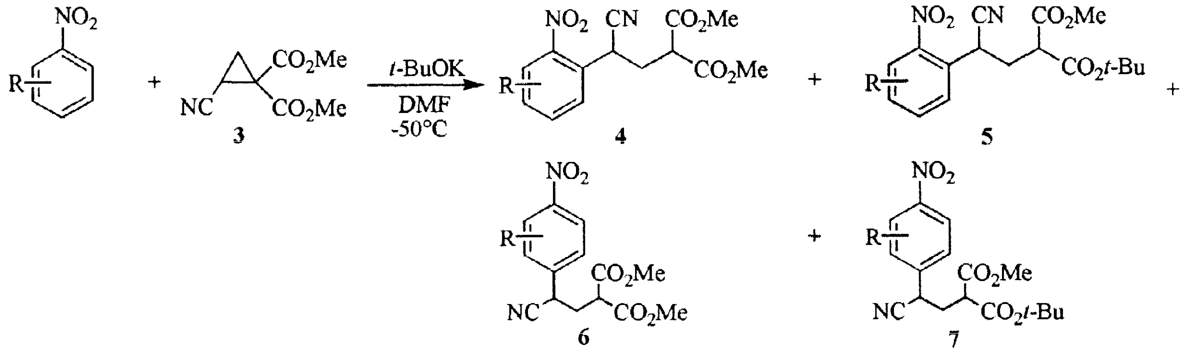
[2] Exceptions are known. For instance successful reactions with electrophiles were reported for hindered cyclopropanecarboxylic acid esters [Haner R, Maetzke T, Seebach D. Helv Chim. Acta 1986; 69: 1655-1665].

[3] General experimental procedure: to a solution of potassium *t*-butoxide (3 mmol) in DMF (5 ml) a solution of nitroarene (1 mmol) and **3** (1 mmol) in DMF (1 ml) was added dropwise at -50°C. The reaction mixture was stirred at -50°C for 10 min. and poured into an ice-cold diluted hydrochloric acid solution. The resulting mixture was extracted with CH_2Cl_2, the extract was washed with water, dried and evaporated. The products (all oils) were isolated by column chromatography and characterized by ^1H NMR, MS and elemental analysis or HRMS.



Scheme 2

$ArNO_2$	$ArNO_2$ recovery	product **4**	product **5**	product **6**	product **7**
4-chloronitrobenzene	19 %	**4a**, 44 %	**5a**, 19%		
4-trifluoromethylnitrobenzene	6 %	**4b**, 35 %	**5b**, 8%		
1-nitronaphthalene[a]	35 %	**4c**, 17%	**5c**, 7 %		
nitrobenzene	11 %	**4d**, 6 %[b]	**5d**, 6 %[b]	**6d**, 6 %[c]	**7d**, 6 %[c]

[a] The reaction was performed at -70°C.

[b] A mixture of **4d** and **5d** was isolated. The ratio **4d** : **5d** was estimated by NMR.

[c] A mixture of **6d** and **7d** was isolated. The ratio **6d** : **7d** was estimated by NMR.

Table 1[4]

identification. Little discrimination between *ortho* and *para* positions in nitrobenzene could be observed, on the other hand nitronaphthalene gave exclusively 2-substituted products **4c** and **5c**. This orientation of the substitution in 1-nitronaphthalene is typical for *secondary* carbanions, whereas tertiary carbanions have been shown to substitute hydrogen in the position 4 [9]. Exclusive formation of **4c** and **5c** seems to indicate diminished steric requirements of the carbanion of **3**, as compared to its open-chain congeners.

Yields were low to moderate and some recovery of the starting nitroarenes was always observed. This can be attributed to self-condensation of **3**, which is extremely unstable under the reaction conditions. This was confirmed by an experiment in which **3** was added to a potassium *t*-butoxide solution in DMF and the reaction mixture was immediately quenched. The ^1H NMR spectrum of the crude product indicated that **3** was totally consumed and a complex mixture of many compounds or a polymeric material was formed. The only identifiable signals were singlets of methyl and *t*-butyl groups and the integration indicated advanced transesterification.

The structures of the products suggest several ways for their utilization, making them interesting intermediates in organic synthesis. One of such possibilities presented itself during experiments aimed at optimization of conditions of the VNS reaction itself. We found that on raising the temperature of the

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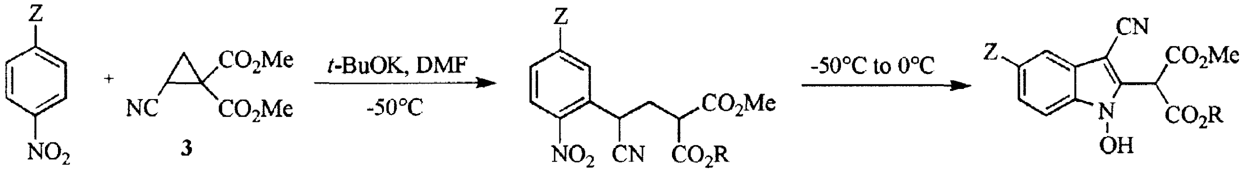
[4] Analytical data of the compounds **4a** and **5a** are given as an example for the series. **4a** ^1H NMR δ_H ($CDCl_3$, 200 MHz): 2.44-2.52 (2H, m,), 3.62 (1H, t, J=7.4), 3.70 (3H, s), 3.76 (3H, s), 4.84 (1H, dd, J=8.3, J=6.8), 7.47 (1H, dd, J=8.8, J=2.2), 7.69 (1H, d, J=2.2), 8.00 (1H, d, J=8.8). MS (LSIMS,m/z) 341, 343 $(M+H)^+$. Elemental analysis - calc. for $C_{14}H_{13}ClN_2O_6$: C 49.35, H 3.85, N 8.22; found C 49.53, H 4.05, N 7.88. **5a** ^1H NMR δ_H ($CDCl_3$, 200 MHz): 1.45 (4.5H, s), 1.50 (4.5H, s) 2.44-2.56 (2H, m,), 3.55-3.62 (1H, m), 3.74 (1.5H, s), 3.81 (1.5H, s), 4.85-4.96 (1H, m), 7.53 (1H, dd, J=8.8, J=2.2), 7.75 (0.5H, d, J=2.2), 7.76 (0.5H, d, J=2.2), 8.06 (1H, d, J=8.8). MS (LSIMS,m/z) 383, 385 $(M+H)^+$. HRMS (LSIMS) - calc. for $C_{17}H_{19}ClN_2O_6+H$: 383.1010; found 383.1010.

reaction mixture, the initially formed products **4a** and **5a**, derived from *p*-chloronitrobenzene, were converted to *N*-hydroxyindoles **8a**[5] and **9a**, respectively. This reaction worked also for *p*-trifluoromethylnitrobenzene leading eventually to *N*-hydroxyindoles **9b** and **9b** bearing trifluoromethyl group on the benzene nucleus. Transformations of this type have been recently described in detail in another publication from our laboratories [10]. The overall yields were rather low but not much lower than the yields of the corresponding VNS reactions themselves. However, compared to the starting materials, the complexity of the products of this one-pot reaction is quite remarkable.



Z=Cl; R=Me: **4a**,
R=*t*-Bu: **5a**

Z=CF$_3$; R=Me: **4b**,
R=*t*-Bu: **5b**

Z=Cl; R=Me: **8a**, 21%
R=*t*-Bu: **9a**, 13%

Z=CF$_3$; R=Me: **8b**, 31%
R=*t*-Bu: **9b**, 8%

Scheme 3

In conclusion, this work has validated the concept of reaction of electrophilic arenes with carbanions derived from electrophilic cyclopropanes. The transformation falls in the category of the ring-opening VNS reactions. It is noteworthy that execution of this kind of VNS reaction has met with limited success so far and only few examples have been known [11]. Also, this is the first example of a VNS reaction proceeding *via* departure of a carbon leaving group. The reaction seems to be general for nitroarenes; however, its scope with respect to cyclopropanes **1** remains to be investigated. If the preparative aspect of the reaction can be improved then it can provide structurally interesting products amenable for further elaboration, including expedient conversion to *N*-hydroxyindoles.

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[5] Compound **8a**: ^{1}H NMR δ_H (CDCl$_3$, 200 MHz): 3.87 (6H, s), 5.23 (1H, s), 7.31 (1H, dd, J=8.8, J=1.9), 7.48 (1H, d, J=8.8), 7.68 (1H, d, J=1.9). MS (EI, m/z) 322, 324 M$^+$. HRMS (EI) - calc. for $C_{14}H_{11}ClN_2O_5$: 322.0356; found 322.0352. Satisfactory spectral data and HRMS were also obtained for the hydroxyindoles **9a**, **8b** and **9b**.