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AN INTRIGUING CASE OF THE RETRO-MICHAEL REACTION

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Abstract: In the course of Michael addition of carbanions, derived from malononitrile or cyanoacetic ester, to a nitrostyrol *retro* reaction has also been observed. Depending on the reaction conditions any of the two compounds formed can be obtained as main product. The entire process has been thoroughly investigated.

Aiming at the synthesis of different heterocyclic derivatives the Michael addition of conjugated carbanions to the double bond of nitrostyrol derivative **1** has been investigated. It was found, that under the conditions applied no reaction of malonester with nitrostyrol **1** took place, however addition of carbanion generated from ethyl cyanoacetate or malononitrile, respectively, resulted in almost total conversion of the nitrostyrol **1**. Best results were attained, when the reaction was carried out in THF or dichloromethane in the presence of KF on basic Al_2O_3[1] as catalyst. Investigating the parameters of the reaction we found that molar ratio of the rectants as well as of the KF used greatly influenced the result of the reaction in question. When, for example, 10 equivalents of ethyl cyanoacetate and 1 equiva-

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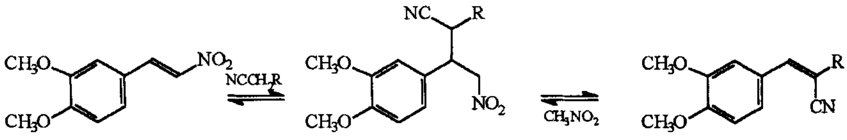
lent of KF/Al_2O_3 were applied in THF, after a 48 hour reaction benzylidenecyanoester **3a**[2] was obtained as main product, besides 10-15% of the desired Michael product **2a**. If the amount of the reactant and base was decreased (**1** : cyanoester : base = 1:2:0.5), however, the product ratio **2a**/**3a** changed dramatically to about 2:1, and the Michael product **2a** could be obtained *via* column chromatography in 65-70% yield. Similar results have been obtained with malononitrile; i.e. according to the conditions used either benzylidenemalononitrile **3b**[2] or Michael product **2b** could be obtained (in about 70% yield after chromatography) as main product.

Since the "substitution" reaction (nitromethane is substituted by compounds containing sufficiently active methylene group) in a Knoevenagel type product, such as nitrostyrol **1**, requires some interpretation, the nature of the reaction has further been investigated. The whole procedure is supposed to be an equilibrium process according to the following scheme:



1

2	R
a	$CO_2C_2H_5$
b	CN

3	R
a	$CO_2C_2H_5$
b	CN

The entire reversibility of the process is supported by the fact, that if **2** is stirred in solution in the presence of KF/Al_2O_3 catalyst, an equilibrium mixture, containing tiny amount (3-4%) of nitrostyrol **1**, low amount (10-15%) of adduct **2** and mainly (70-80%) benzylidene compound **3**, is obtained. The same ratio of the components **1**, **2** and **3** is attained, if **3** is reacted with equimolar amount of nitromethane or **1** with equimolar amount of cyanoester or malononitrile, respectively, if time long enough (48h) and catalyst (2eq) are assured. Decreasing the amount of the catalyst requires longer reaction time to reach the equilibrium. The position of the equilibrium, of course, could well be influenced by increasing the amount of the reactants; the presence of excess (10eq) nitromethane in the mixture, for example, results in significant increase (>70%) of the desired adduct **2**.

Accordingly good yield (~75%) of **2a** and **2b** was attained from common starting material nitrostyrol **1**, when it was reacted with the proper reactant, and after its almost total disappearance (~3 h) excess nitromethane is added into the mixture and left to equilibrate (24-48 h).

Similar reverse processes have already been reviewed[3] and observed with nitro-stilbenes[4], however the above described case is the first in which all three members of a complex equilibrium system were isolated and interconverted, and the position of the equilibrium influenced.

Experimental

General Procedure for Michael Reaction

To a solution of nitrostyrol **1** (0.48g; 2 mM) in dichloromethane or tetrahydrofurane (60 ml) ethyl cyanoacetate or malonodinitrile and freshly prepared or activated KF on basic alumina[1] (amounts are summarized in the Table below) were admixed and stirred under argon atmosphere for 3 - 20 hours at ambient temperature. When no further change can be observed (TLC investigation on Polygram Sil G/UV$_{254}$ pre-coated plastic sheets, eluent system: dichloromethane - hexane - ethylacetate 10:5:1; Rf **1**>**3**>**2**;) the catalyst was filtered off, the solution evaporated in *vacuo* and the residue separated on column (Kieselgel 60, mesh 0.063-0.200 in the above eluent mixture).

2a: Ethyl 2-cyano-3-(3′,4′-dimethoxyphenyl)-4-nitro-butyrate was obtained as a syrup (a 3:2 diastereomeric mixture of the *erythro* and *threo* isomers) in 65-70%

Table

Starting material		Reagent		KF/Al_2O_3	T	Components %		
compound	mmol	compound	mmol	mmol	h	**1**	**2**	**3**
1	2	$NCCH_2CO_2Et$	20	2	48	5	20	75[a]
1	2	$NCCH_2CO_2Et$	4	0.5	24	5	80[b]	15
1	2	$NCCH_2CN$	4	0.5	6	6-7	80[b]	14
1	2	$NCCH_2CN$	4	2	48	5	15	80
1	2	$NCCH_2CN$	10	2	24	4	20	75
2a	1	-	-	1	48	5	15	80
3a	2	CH_3NO_2	20	2	48	5	70	25
3a	2	CH_3NO_2	40	2	48	5	85[c]	10
1	3	$NCCH_2CO_2Et$	12	3	3			
		+ CH_3NO_2	60	3	48	5	85[c]	10

[a] **3a** has been isolated in 60% yield after chromatography
[b] **2a** and **2b** have been isolated in 70% yield after chromatography
[c] **2a** has been isolated in 77% yield after chromatography

yield. IR(film): ν(cm^{-1}): 1380, 1510 and 1555 (NO_2), 1635 (C=O), 2240 (CN), 2830 (OCH_3); ^{1}H-NMR ($CDCl_3$) δ (ppm): *erythro* 1.18t + 4.15q (*J*=7.1Hz, OCH_2CH_3), 3.87s and 3.89s (2×OCH_3), 4.10d (*J*=5.6Hz, C*H*CNCO$_2$Et), 4.19ddd (*J*= 8.5, 6.3 and 5.6Hz, Ar-C*H*), 4.82 and 4.92 (ABX system, J_{gem}= -13.6, J_{vic}= 6.3 and 8.5, resp., C*H*$_2$NO$_2$), 6.80-6.92m (aromatic protons); *threo* 1.26t + 4.12q (*J*=7.1Hz, OCH_2CH_3), 3.87s + 3.89s (2×OCH_3), 3.92d (*J*=5.4Hz, C*H*CNCO$_2$Et), ~4.20m (Ar-C*H*), 4.91 and 5.00 (ABX system, J_{gem}= -13.4, J_{vic}= 6.3 and 8.0, resp., C*H*$_2$NO$_2$), 6.80-6.92m (aromatic protons); Analysis: calculated C 55.89%, H 5.63%; N 8.69%, found C 56.04%, H5.71 %, N 8.57%.

2b: 2-Cyano-3-(3′,4′-dimethoxyphenyl)-4-nitro-butyronitrile was obtained as colourless crystals (65-70% yield), mp: 97-98 °C (diethyl ether). IR(KBr): ν(cm^{-1}): 1380, 1520 and 1560 (NO_2), 2260 (CN), 2840 (OCH_3); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.90s and 3.91s (2×OCH_3), 4.04ddd (*J*=7.9, 6.0 and 5.6Hz, Ar-C*H*), 4.42d [*J*=5.6Hz, C*H*(CN)$_2$], 4.90 and 4.96 (ABX system, J_{gem}= -13.8, J_{vic}= 6.0 and 7.9, resp., CH_2NO$_2$), 6.83br s (C2′-H), 6.89-6.94m (C5′-H and C6′-H); Analysis: calculated C 56.72%, H 4.76%, N 15.27%; found C 56.65%, H 4.88%, N 15.14%.

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