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NEW SUBSTITUTION REACTION OF ALLYLIC NITRO COMPOUNDS. REGIOSELECTIVE REPLACEMENT OF NITRO GROUP IN CYCLIC α-(NITROALKYL)ENONES BY NUCLEOPHILES

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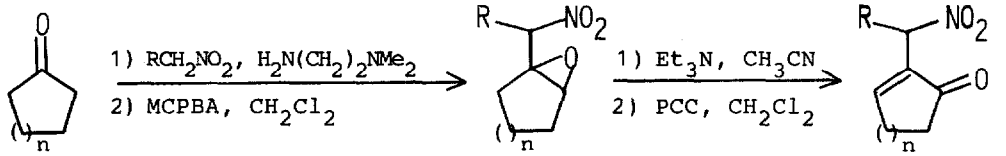
Summary: Regioselective replacement of nitro group in cyclic α-(nitroalkyl)-enones by various nucleophiles such as stabilized carbanions, amine, NaN_3, $PhSO_2Na$ and PhSNa provides the overall S_N2 type products.

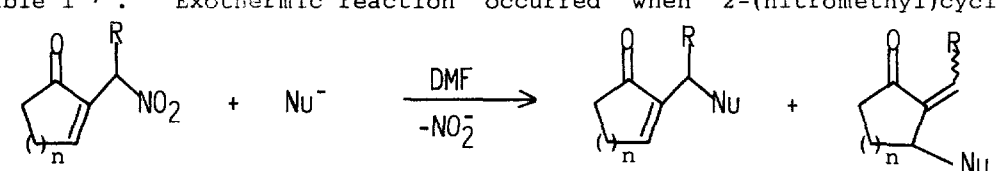
Over the past several years allylic nitro compounds have proved to undergo the replacement of nitro group by various nucleophiles with the aid of metal catalysts such as Pd(0)-phosphine complexes[1], $SnCl_4$ and $TiCl_4$[2]. These substitution reactions have opened up a new area of aliphatic nitro compound chemistry. Here we describe a novel and uncatalyzed substitution reaction of allylic nitro compounds, in which cyclic α-(nitroalkyl)enones are the reactive substrates, and carbon, nitrogen and sulfur nucleophiles are involved as reagents.

The requisite α-(nitroalkyl)enones were readily available from cyclic ketones as illustrated in eq 1[3,4]. First we attempted the regiocontrolled



(1)

replacement of nitro group by soft carbon nucleophiles using Pd-phosphine catalyst. Contrary to our expectation, it was found that the highly regio-selective substitution occurred smoothly irrespective of the presence of the catalyst resulting in the S_N2 type products exclusively as shown in eq 2 and Table I[5,6]. Exothermic reaction occurred when 2-(nitromethyl)cyclohexenone



(2)

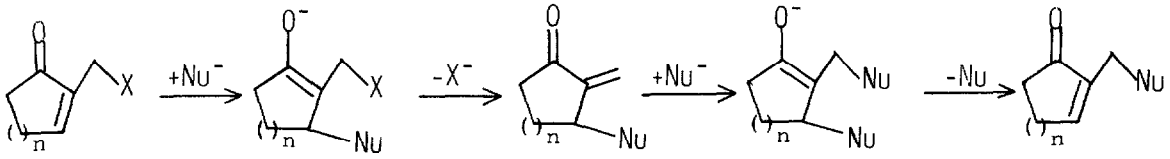
1, R=H, n=2; **2**, R=Me, n=2;
3, R=H, n=1 **4** **5**

(**1**) was added to methyl sodiocyanoacetate in DMF at room temperature. Within 30 min the disappearance of **1** was noted and the S_N2 product **4** was obtained in 48 % yield (entry 1). Although the mass balance was not satisfactory, neither

the S_N2' regioisomer (**5**) nor a stepwise S_N2' substitution-conjugate addition product could be detected. Sterically hindered ethyl sodio-2-cyanobutanoate gave the better yield of product (72 %) (entry 2), while the use of more hindered α-cyanoester resulted in the rather decreased yield (entry 3). With respect to other carbon nucleophiles, the bulkier the carbanion, the lesser the yield (entries 5 and 6).

Interestingly, the use of sterically crowded 2-(nitroethyl)cyclohexenone (**2**) with less hindered carbanions led to the products in better yields than from **1** (entries 1, 7 and 4, 9). Noteworthy is the reaction of **2** with dimethyl sodiomalonate in which two regioisomers were obtained in a 56/44 ratio of S_N2 (**4**) to S_N2' (**5**) product (entry 9). In order to shed light on the observed regiochemistry and on the general reaction mechanism, both the S_N2 and S_N2' regioisomers were separated and then treated with the same carbanion in DMF, respectively. Considerable conversion of the S_N2' isomer to the S_N2 one was observed with elapse of time, whereas no detectable transformation of the S_N2 isomer to the S_N2' one occurred at all. This fact constitutes a significant evidence for the view that the formation of the S_N2 product is ascribed to the consecutive two S_N2' reactions via addition-elimination sequence of nucleophile to the enone systems so as to give the thermodynamically stable product as depicted in Scheme 1 (X=NO_2).

Scheme 1

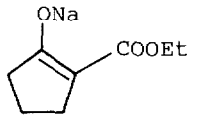


6

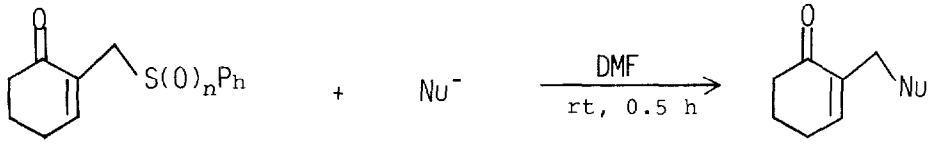
It was anticipated that other reagents possessing both nucleophilicity and leaving ability would effect similar reactions. Indeed, secondary amine, NaN_3, $PhSO_2Na$ and PhSNa were found to be suitable nucleophiles as exemplified in Table I, giving the S_N2 products exclusively[5,6,7]. 2-(Nitromethyl)cyclopentenone (**3**) was also an active substrate (Table I).

Interestingly, we found that the substrate which could undergo the regioselective replacement mentioned above was not limited to α-(nitroalkyl)enones. Both 2-(phenylsulfonylmethyl)- and 2-(phenylsulfenylmethyl)cyclohexenone (**8** and **7**) were reacted with ethyl sodio-2-cyanobutanoate in DMF to provide the same S_N2 product (eq 3). 2-(Piperidinomethyl)cyclohexenone was inert to the reaction conditions. Furthermore, treatment of **8** with PhSNa in DMF led to the formation of **7**; formal reduction of the sulfone to the corresponding sulfide was achieved (eq 3)[8]. These facts indicate that the addition-elimination sequence of nucleophile to the enones (Scheme 1) rather than the direct S_N2 replacement or the S_N2' reaction followed by intramolecular allylic rearrangement[9] is also likely to take place in the reaction of substrate **7** and **8**, and that in general the leaving ability of functional group (X) in **6** seems to be

Table I. Reaction of 2-(nitroalkyl)cycloalkenones with nucleophiles (eq 2)[6].

entry	nitro enone	Nu^-	time (h)	product	yield (%)[a]
1	**1** (R=H,n=2)	NaCH(CN)COOMe	0.5	**4**	48
2	**1**	NaEtC(CN)COOEt	0.5	**4**	72
3	**1**	Na*i*-PrC(CN)COOMe	2.0	**4**	53
4	**1**	$NaCH(COOMe)_2$	0.5	**4**	57
5	**1**	$NaMeC(COOMe)_2$	24	**4**	10
6	**1**		24	**4**	12
7	**2** (R=Me,n=2)	NaCH(CN)COOMe	1.5	**4**	70
8	**2**	Na*i*-PrC(CN)COOMe	4.0	**4**	23
9	**2**	$NaCH(COOMe)_2$	1.5	**4** : **5**[b] (56:44)	73
10	**3**	piperidine	1.0	**4**	56[c]
11	**1**	piperidine	1.0	**4**	83[c]
12	**3** (R=H,n=1)	NaN_3	0.5	**4**	73
13	**1**	NaN_3	0.5	**4**	79
14	**3**	NaSPh	0.5	**4**	88
15	**1**	NaSPh	0.5	**4**	83
16	**2**	NaSPh	0.5	**4**	94
17	**3**	$NaSO_2Ph \cdot 2H_2O$	0.5	**4**	72
18	**1**	$NaSO_2Ph \cdot 2H_2O$	0.5	**4**	75
19	**2**	$NaSO_2Ph \cdot 2H_2O$	0.5	**4**	75

a) Isolated yield. b) E/Z = 20/80. c) Reaction was run in acetonitrile.



(3)

7, n=0	Nu^-=	NaEtC(CN)COOEt	55 %
8, n=2		NaEtC(CN)COOEt	61
8		NaSPh	92

responsible for the overall reactivity of enones. Although a series of competition experiments of a combination of two among the enones **1**, **7** and **8** are infeasible owing to the complication of the experimental results by the eliminated X^- (see Table I and eq 3), it is easily deduced from the above results that the decreasing order of relative reactivity of the enones (**6**) toward nucleophiles is as follows: **X = NO_2 > SO_2Ph > SPh >> NR_2**. Thus, the above mentioned regioselective substitution reaction turned out to be a general process for various cyclic enones bearing a leaving group at the β' position

like **6**[10].

Results described here attest to the ease of availability, the high reactivity, and the synthetic utility of cyclic α-(nitroalkyl)enones. Particularly, these substrates have proved to undergo overall S_N2 replacement of nitro group by various soft nucleophiles with high regioselectivity through the consecutive two S_N2' reactions to afford β'-functionallized cyclic enones which can be utilized for further synthetic manipulation. Further studies on the scope and limitation as well as the synthetic application of this reaction will be reported in due course.

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3) Tamura, R.; Sato, M.; Oda, D. J. Org. Chem. **1986**, 51, 4368.

4) Tamura, R.; Kato, M.; Saegusa, K.; Oda, D.; Egawa, T.; Yamamoto, T. J. Org. Chem. **1987**, 52, 1640.

5) All new compounds have been fully characterized by spectral means and combustion analysis.

6) The reaction in Table I were carried out in the following manner. To the nucleophile (1.5 mmol) in DMF (3 mL) was added a solution of the substrate (1.0 mmol) in DMF (1 mL). The resulting mixture was stirred at 25 °C for the stated period of time and partitioned between ether and water. The ether extract were washed with saturated brine and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Products were purified by column chromatography on silica gel.

7) Simple allylic nitro compounds were reported to react with PhSNa in HMPA at 50 °C to provide allylic sulfides. Ono, N.; Hamamoto, I.; Yanai, T.; Kaji, A. J. Chem. Soc., Chem. Commun. **1985**, 523. The present regioselective denitro-sulfenylation reaction of α-(nitroalkyl)enones proceeded under quite mild conditions; the employment of PhSH-Et_3N-CH_3CN system (at 25 °C for 0.5 hr) instead of PhSNa-DMF in the reaction of entries 14 to 16 in Table I led to the same products in comparable yields.

8) It was recently reported that the addition of 1,ω-alkanedithiols to certain (hydroxyethylsulfonyl)methylenones resulted in the formation of sulfur-containing macrocycles through consecutive Michael reactions. Brocchini, S.J.; Eberle, M.; Lawton, R.G. J. Am. Chem. Soc. **1988**, 110, 5211.

9) A similar overall S_N2 attack stemming from the consecutive two S_N2' reactions was observed in the reaction of 4-bromo-3-phenylsulfonylbutene with aniline or thiolates. Auvray, P.; Knochel, P.; Normant, J.F. Tetrahedron **1988**, 44, 6095.

10) Acyclic allylic compounds CH_2=C(EWG)CH_2X bearing an electron-withdrawing group (EWG) and a good leaving group (X) like Cl, Br, NMe_3, or $OCOCMe_3$ are known as multi-coupling reagents to undergo sequential alkylation with reactive carbon nucleophiles such as enamines, ketone enolates and cuprates through consecutive Michael reactions. (a) Nelson, R.P.; McEuen, J.M.; Lawton, R.G. J. Org. Chem. **1969**, 34, 1225. (b) Seebach, D.; Knochel, P. Helv. Chim. Acta **1984**, 67, 261 and references cited therein. (c) Auvray, P.; Knochel, P.; Normant, J.F. Tetrahedron **1988**, 44, 4495; 4509 and references cited therein. Also see ref 8 and 9.

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