Tandem *in situ* Generation of Azomethine Ylides and Nitro-ethylene: Synthesis of 3-Unsubstituted-4-nitro-pyrrolidines

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The potential of the simplest nitro-olefin, nitro-ethylene as a versatile reagent for organic synthesis has found a limited application. This useful C-C-N synthon, which was described first early in this century by *Wieland* and *Sakkelarios*[1] is known to polymerize readily in the presence of any trace of water and to react violently with base. This behaviour prevents its use in many kind of reactions. In spite of this sensitivity the nitro-ethylene itself has been applied as a very electron-deficient and highly reactive dienophile in Diels-Alder reactions with electron-rich[2] or unactivated[3] dienes and also as a useful acceptor for nucleophilic radicals.[4] A wide variety of nucleophiles were used in conjugate additions to nitroethylene.[5] A broad study[6] concerned about avoiding the facile base-mediated polymerization in these cases, which was crucial to the successful application of these additions in the synthesis of important natural products.[5k,l]

Nitroethylene is also a good dipolarophile in 1,3-dipolar cycloadditions, but only a few example has been published to date: the reaction with 9-diaza-fluorene led to a nitrocyclopropane derivative,[7] while the reaction with 1-azidoadamantene gave an 1H-1,2,3-triazole[8] by the further reaction of the original cycloadduct in both cases. An interesting observation being rationalized from FMO considerations, is that the regiochemistry of nitroethylene reactions with nitrones[9] and nitrile oxides[10] is often reversed from that observed with less electron deficient alkenes.[11]

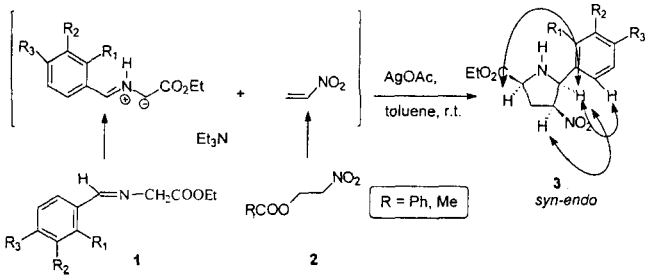
However there is no report on the cycloadditions of such important 1,3-dipoles, azomethine ylides, or nitrile ylides, to nitroethylene. It might have been mostly due to the base-related generation of these unstable species. As a palliative to the difficulty in handling and storing the very base sensitive nitro-ethylene we considered the possibilty of employing some more convenient surrogates. In connection with our studies on the synthesis of biologically active pyrrolidine alkaloids we describe here the tandem *in situ* generation of azomethine ylides and nitroethylene. This process leads in one step steresoselectively to 3-unsubstituted-4-nitro-pyrrolidine cycloadducts.

There are many reports in the literature on the base catalyzed formation of azomethine ylides[12] and we have also some experience with this kind of reaction.[13] In contrast, a few reports on the thermal *in situ* generation and reaction of nitro-ethylene are known: 2-nitroethyl phenyl sulfoxide[14], 2-benzyloxy-[5f,i] or 2-acetoxy-nitroethane[5a-d] and from nitroethanol in the presence of dehydrating agent.[3a]

We have decided to study the behaviour of 2-acetoxy-nitroethane in the presence of triethylamine and of an azomethine ylide generated also by the action of the same base. Under the basic reaction conditions β-elimination of the acetate group would generate the requisite nitro-ethylene *in situ*, furthermore, the concentration of the latter could be maintained sufficiently low to minimize base induced polymerization. The imine precursors for the dipoles were prepared using the standard method[15] from aromatic aldehydes and glycine ester, while the 2-acetoxy-nitroethane was obtained by the simple acylation of 2-nitro-ethanol with acetic anhydride.[5b]

The cycloaddition reactions were carried out in dry toluene as a solvent using silver acetate as a catalyst to avoid formation of the isomeric azomethine ylides and the Michael addition products, well known from the earlier investigations (Scheme 1).

The cycloadditions gave the expected products in all cases as a single isomer in a moderate yield. The results are summarized in Table 1 and 2. The lower temperature decreased the yield (Table 1, entry 2), while the excess of dipolarophile (Table 1, entry 7) only effect the amount of polymeric by-



Scheme 1

Table 1 The results of the cycloadditions under different conditions

Entry	base (equiv.)	temp.	**2** R = (equiv.)	product[a]	Yield[b]
1	Et_3N (2)	0 °C	Me (1)	**3a**	42 %
2	Et_3N (2)	-78 °C	Me (1)	**3a**	22 %
3	Et_3N (2)	0 °C→ r.t	Me (1.2)	**3a**	55 %
4	Et_3N (1)	0 °C→ r.t	Me (1.2)	**3a**	8 %
5	Et_3N (2)	r.t.	Ph (1)	**3a**	15 %
6	Et_3N (2)	0 °C	Ph (1.5)	**3a**	12 %
7	Et_3N (2)	0 °C	Me (2.5)	**3a**	44 %

[a]Chemical yields after column chromatography. [b]R_1=R_2=R_3=H.

Table 2 The chemical yields of the cycloadditions under the conditions described in the general procedure

Entry	product	R_1	R_2	R_3	Yield[a]
1	**3b**	H	H	OMe	56%
2	**3c**	Cl	H	Cl	64%
3	**3d**	H	H	CH_3	54%
4	**3e**	H	H	Cl	55%
5	**3f**	H	H	CF_3	62%
6	**3g**	CH_3	H	H	58%
7	**3h**	OMe	OMe	H	54%

[a]Chemical yields after column chromatography.

Table 3 Selected ^1H and ^{13}C n.m.r. chemical shifts, H-H couplings and measured n.O.e. connectivities for compound **3c**

	δH	[$J_{H,H}$ (Hz)]	$^1H\{^1H\}$ n.O.e.[a]		δC
H-4	5.44 dd	$J_{3,4}$ = 2.4	H-5, **H-3**	C-4	86.2
H-5	4.85 dd	$J_{4,5}$ = 6.4	Ar-6'H, H-4, H-2	C-5	64.5
H-2	4.04 dd	$J_{2,3}$ = 6.3 and 9.4	H-3, H-5	C-2	58.4

[a]Different characters are used as follows, normal: medium enhancement (2% < n.O.e.< 6%); bold: strong enhancement (n.O.e. >5%).

products arising from the anionic polymerizzation of the nitro-ethylene. These impurities and the unreacted imine were separated in all the cases easily by column chromatogrpahy. The use of different nitro-ethylene source (entries 5, 6) or other base (DABCO, DBU) does not improve the results. The substituents on the aromatic ring do not have any effect on the yield (Table 2) .

The structure and stereochemistry of the cycloadducts were confirmed by HH-COSY and n.O.e. experiments. This showed clearly the formation the "normal" regioisomer. The *syn*-azomethine ylide reacted with the nitro-ethylene through the most preferred *endo* transition state to give the *all-cis* cycloadduct as summarised in Table 3 for adduct **3c**.

The cycloadducts are prone to epimerize at position 4 upon standing in solution due to the strongly activated nature of the proton adjacent to the nitro-group. After several days all of them epimerized giving the 1 : 1 mixture of *endo* and *exo* products.

In conclusion the method reported here provides a fairly general and mild method by the tandem in situ generation of 1,3-dipole and nitro-ethylene for the preparation of 4-nitro-pyrrolidines, although the yields only rarely exceed the modest.

1,3-Dipolar cycloadditions between ethyl (arylideneamino)acetates and nitroethylene generated *in situ*. - *General procedure:* 10 mmol of ethyl (arylideneamino)acetate and 12 mmol of 2-acetoxy-nitroethanol were dissolved in 50 mL dry toluene then 2.5 g (15 mmol) AgOAc and MS A4 were added. The reaction mixture was cooled down to 0 °C and triethylamine (2.8 mL, 20 mmol) was added slowly to the well stirred reaction mixture. After 10 min at 0 °C it was allowed to warm up to room temperature. When the reaction was completed (judged by TLC) 25 mL saturated aqueous ammonium chloride was added, the precipitate was filtered off and the residue was extracted with ether. The combined organic fractions were dried over magnesium sulfate, evaporated and the residue was purified by column chromatography to yield the cycloadducts.

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