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On the behavior of bis(sulfonyl)nitrobutadienes towards primary amines: a convenient access to 1-alkyl-2-aryl-4-(phenylsulfonyl) pyrroles

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ABSTRACT

The conjugated bis(sulfonyl)nitrobutadienes **1** undergo, with primary amines, competitive $MeSO_2$ replacement [vinylic substitution at C(1)] versus aza-Michael addition to the nitroethenyl C(3)–C(4) double bond. The latter pathway eventually leads to the trisubstituted pyrroles **2** and conditions have been optimized in order to maximize the yield of such polyfunctionalized heterocycles. Interestingly, in trifluoroethanol tetrasubstituted pyrroles **7** are also formed, thanks to a final aromatization via oxidation by 'endogenous' nitrite.

1. Introduction

Aza-heterocycles are certainly compounds of outstanding interest from a biological, pharmacological and, broadly speaking, applicative point of view: accordingly new synthetic approaches are continuously investigated, as testified by the gigantic number of papers which appear every year in the literature.[1]

Within our long-standing project centered on the synthetic versatility of nitrobutadiene building-blocks deriving from the initial ring-opening of adequately functionalized nitrothiophenes,[2,3] one of the privileged targets throughout has been the recognition of convenient high-yielding, atom-economic, possibly metal-free processes able to build-up heterocycles of different nature, size and structure: a goal that can be reached, for instance, when finely modulating the reactivity of nitrobutadienes by means of a careful choice of type, number and position of substituents on the diene frame or the employment of suitable reagents and/or experimental conditions. Both S-[4] and N-heterocycles can thus be effectively prepared: as far as the latter are concerned, besides earlier reports from our laboratory,[5] the preparation of polysubstituted pyrazoles,[6] pyridazines,[6a,7] isoxazolines,[6b] carbazoles[8] and N-fused pyrroles[9] has been more recently successfully accomplished.

A few years ago we reported that the reaction of symmetrical 2,3-dinitro-1,3-butadienes with primary amines in 1:1 CH_2Cl_2/MeOH is a useful approach to polysubstituted pyrrolidines and to pyrrolines and pyrroles therefrom (Scheme 1).[10] The process involves a double aza-Michael addition, the second of which very effectively leading, notwithstanding a disfavored 5-*endo*-*trig* cyclization, to the pyrrolidine ring.

Herein we report on the behavior of unsymmetrical bis(sulfonyl) nitrobutadienes (obtained from the initial ring-opening of 3-phenylsulfonyl-4-nitrothiophene with pyrrolidine)[11] towards primary amines: the observed competition leading to results endowed with both mechanistic and synthetic interest.

2. Results and discussion

Preliminary tests were carried out on the model reaction of 1-methylsulfonyl-3-nitro-2-phenylsulfonyl-4-*p*-tolylbutadiene (**1a**) with butylamine in the experimental conditions previously adopted for the reaction in Scheme 1, i.e., 3.3 equiv of amine in 1:1 CH_2Cl_2/MeOH at room temperature.[10] Interestingly enough, rather unexpectedly, under such conditions two products could be

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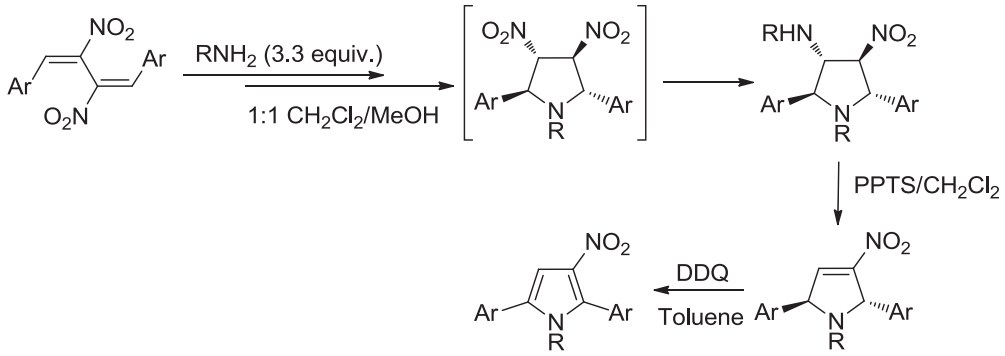
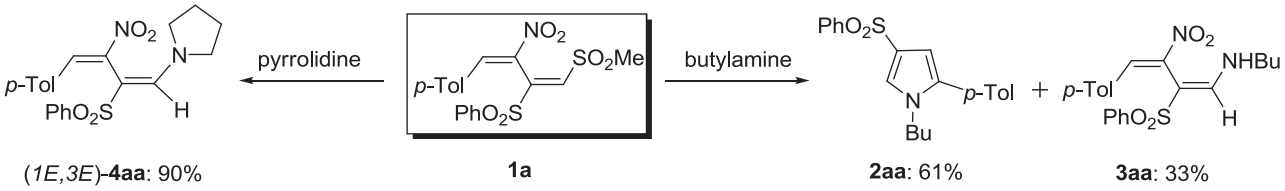


Scheme 1. 5-Membered N-heterocycles from 1,4-diaryl-2,3-dinitro-1,3-butadienes and primary amines.[10]



Reaction conditions: 1:1 CH_2Cl_2/MeOH, r.t., 1 h; amine: 3.3 mol equiv.

Scheme 2. Results of the reaction of nitrobutadiene **1a** with model primary and secondary amines.

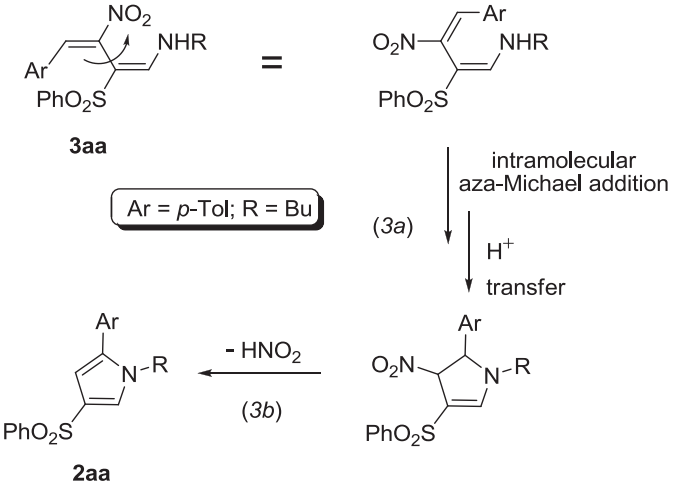
isolated (Scheme 2; entry 2 of Table 1), viz. the appealing 1,2,4-trisubstituted pyrrole **2aa**, as the main product in a definitely rewarding 61% yield, and **3aa** (33%), as the straightforward result of a selective nucleophilic vinylic substitution (S_NV) on the terminal carbon of the bis(sulfonyl)substituted double bond. For the sake of comparison, when reacted with the secondary amine pyrrolidine under the same conditions, **1a** exclusively led to the diene **4aa** (90%), i.e., the substitution product analogous to **3aa** (Scheme 2), through a highly selective and efficient S_NV process which stoichiometrically consumes 2 equiv of amine: accordingly, no significant change in the yield of **4aa** was observed on switching from 3.3 to 2.2 equiv of pyrrolidine.

From a mechanistic point of view, the formation of **2aa** could be the result of different conceivable reaction pathways. For instance, it could originate via a follow-up process from the substitution product **3aa** (Scheme 3), whereby an intramolecular aza-Michael addition (step *3a*) would be followed by aromatization through amine-promoted HNO_2 elimination (step *3b*).

Table 1
Results from reactions of **1a** with butylamine under different experimental conditions

Exp.	Solvent	$BuNH_2$ (molar equiv)	T (°C)	*t* (h)	**2aa** (%)	**3aa** (%)
1	1:1 CH_2Cl_2/MeOH	2.2	rt	1	42	54
2	"	3.3	rt	1	61	33
3	"	6.6	rt	1	76	18
4	"	1.1+1.1 K_2CO_3	rt	1	30	51
5	"	1.1+1.1 TEA	rt	1	37	56
6	"	1.1+5.5 TEA	rt	1	81	16
7	"	3.3	50 °C	0.5	45	36
8	"	6.6	45 °C	1	66	—
9	"	3.3	−50 °C	24	44	29
10	"	"	−78 °C	24	34 (49)[a]	20 (29)[a]
11	CH_2Cl_2	"	rt	1	64	10
12	MeOH	"	rt	2	75	9
13	TFE[b]	"	rt	1	85[c]	8
14	"	6.6	rt	1	71[d]	—

[a] Unreacted substrate **1a** (30%) also recovered (the yield in parentheses refers to the reacted substrate).
[b] Trifluoroethanol.
[c] 4% of the tetrasubstituted pyrrole **7aa** (see text) also isolated.
[d] 20% of the tetrasubstituted pyrrole **7aa** (see text) also isolated.



Scheme 3. Mechanistic hypothesis for the formation of pyrroles **2** through dienes **3**.

As a matter of fact, the treatment of isolated **3aa** with 1 equiv of butylamine in 1:1 CH_2Cl_2/MeOH at room temperature did lead to the formation of some **2aa**, although in definitely longer reaction times (40% after 4 days, with some unreacted **3aa** still present in a rather complex final mixture). The sluggishness of any 'direct' **3aa** to **2aa** conversion cannot be attributed, on the other hand, to the need for configurational isomerization of **3aa** in order to attain the correct spatial arrangement for an effective intramolecular nitrogen attack onto C(4). This is because the isolated diene already has the required *E*-configuration at the C(1)–C(2) double bond (cf. the ORTEP drawing in Fig. 1a, relevant to the ethylamino derivative **3ac**, which provided the most suitable crystals for X-ray analysis; for