Tetrahedron 73 (2017) 3147–3152

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Reactivity and substituent effects in the cyclization of *N*-aryl-2-nitrosoanilines to phenazines

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ARTICLE INFO

Article history:
Received 28 December 2016
Received in revised form
3 April 2017
Accepted 20 April 2017
Available online 24 April 2017

Keywords:
Cyclization
Nitroso group
Heterocyclic compounds

ABSTRACT

Reactivity of variously substituted *N*-aryl-2-nitrosoanilines in the reaction of cyclization leading to phenazine derivatives, carried out in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA), was estimated on the base of the observed reaction times. A strong opposite effect of substituents located at position *para* to the nitroso group and those located *para* to the amino group in the side ring was observed. Mechanistic explanation, based on the electronic properties of the substituents and their mesomeric effects, was presented. The usefulness of the obtained data for the designed syntheses of phenazines was exposed.

1. Introduction

Phenazine, its substituted derivatives as well as various aza analogues have been isolated from natural materials and synthesized for more than one hundred years. Nevertheless, due to their important occurrence as a core in both natural and synthetic compounds of valuable biological activity, interest in developing new methods for the synthesis of phenazine derivatives seems not to be falling.[1] Numerous methods for the synthesis of substituted phenazines have been reported, however, they have several limitations, thus can not be considered as being generally applicable.[1,2] This is because most of them are restricted to a narrow collection of substituents and/or a specific substitution pattern of the target phenazine system. Two general strategies, with their numerous variants, are now commonly employed. One of them is based on the condensation of *ortho*-arylenediamines[3] or benzofuroxans[4] with the other suitably functionalized aromatic reagent. The second one, which is more popular, relies on intramolecular cyclization of diarylamine derivatives, *ortho*-substituted with appropriate nitrogen functions. such as NH_2 or NO_2. The cyclization process can occur, depending on the oxidation state of that group, as oxidative[5] or reductive[1e,6] process. The starting diarylamines are usually obtained from appropriate *ortho*-halogenonitroarenes, which is often not an easy task. In some older methods either they, or their oxidized forms, can be considered as unstable intermediates. This is the case of the Wohl-Aue reaction,[7] where under strong basic conditions nitrobenzene condenses with aniline to form phenazine, and the accepted mechanism of which assumes formation of 2-nitrosodiphenylamine as direct intermediate in the cyclization.[7b] The reaction could be attractive as it consists of only one step, and involves easy procedure starting from simple and available substrates. However, reaction conditions are harsh and strongly basic, the yields are low to moderate and the desired products are accompanied with *N*-oxides and significant amounts of by-products.[8] Therefore, the reaction has never found extensive application. The situation has changed entirely after it was revealed that this two-step reaction can be divided into two separate steps, both carried out under optimized conditions. In 2008 we demonstrated that when the anilide anion generated by *t*-BuOK in THF or DMF at low temperature reacts with nitroarenes, nucleophilic substitution of *ortho* hydrogen[9] leads to *N*-aryl-2-nitrosoanilines as ultimate products.[10] These compounds were then found to be versatile starting materials for the synthesis of various nitrogen heterocyclic systems.[11] Particularly, cyclization to phenazine derivatives can be, under selected reaction conditions, accomplished efficiently. Reaction systems such as K_2CO_3 in MeOH, acetic acid as a protic acid, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a silylating agent were found to be effective in that respect.[12] The latter, known for its promoting role in the formation of nitrogen heterocycles, apparently proceeding via intermediate nitrosoarenes,[13] was found to be the most reliable and selective.[12,14]

On the other hand, despite the high yields of the products, we

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http://dx.doi.org/10.1016/j.tet.2017.04.046
0040-4020/

have noticed remarkable differences in rates of the reactions for various starting materials. It seems to be important for the practical synthesis of phenazine derivatives to correlate the speed of the reaction with the structure of the starting nitrosoaniline, in order to determine the limits of their practical applications, and to shed light on the mechanism of the cyclization.

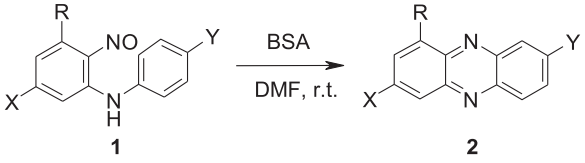
2. Results and discussion

In order to attain the above goal a number of suitable nitrosoanilines **1** were synthesized. A few typical substituents were selected and placed in position 5 (substituent X) or in position 4' (substituent Y) of **1** (Table 1). Their number was limited but their properties range from electron-withdrawing to electron-donating. The reactions were carried out under standard conditions (see experimental part) and monitored by TLC up to the apparent disappearance of the starting material spot visible under UV lamp. Standard work-up allowed to determine the yield of the product, thus, to verify conversion of the reaction. The amount of **1**, if recovered, did not exceed 5%. Because of the procedure used it is obvious that the results are rough, and that they are not suitable for kinetic estimations or calculations. Nevertheless, due to very broad range of the observed reaction times and their monotonic, strong dependence on the electronic properties of the substituents, the results are enlightening, and provide information about the course of the reaction under consideration.

Cyclization of 2-nitrosoanilines possessing different substituents X at position 5 (**1a-f**) is quite fast for a strong electron-withdrawing group X = CF_3, slower for weaker EWG such as halogens, and very slow for X = EDG which is able to donate electron pairs. The differences are huge, so that *N*-(4-chlorophenyl)-5-dimethylamino-2-nitrosoaniline (**1f**) practically did not react at all under the conditions applied.

The results collected in Table 1 may be specially helpful for designing of the synthesis of specific phenazine derivatives. Formally any unsymmetrically substituted phenazine can be obtained from two, conversely substituted *N*-aryl-2-nitrosoanilines.[12]

Table 1
Cyclization of nitrosoanilines **1** to phenazine derivatives **2**.



1 **2**

Entry	Nitrosoaniline				Reaction time[a] h	Phenazine	
	1	R	X	Y		**2**	Yield[b] %
1	**1a**	H	CF_3	Cl	0.5	**2a**	82
2	**1b**	H	H	Cl	23	**2b**	90
3	**1c**	H	Cl	Cl	48	**2c**	89
4	**1d**	H	F	Cl	48	**2d**	87
5	**1e**	H	OMe	Cl	480	**2e**	92
6	**1f**	H	NMe_2	Cl	360[c]	**2f**	traces
7	**1g**	H	Cl	NMe_2	0.5	**2f**	90
8	**1h**	H	Cl	OMe	0.5	**2e**	86
9	**1i**	H	Cl	H	48	**2b**	93
10	**1j**	H	Cl	CN	360	**2g**	85
11	**1k**	Cl	Cl	OEt	0.5	**2h**	91
12	**1l**	Cl	Cl	Cl	36	**2i**	87
13	**1m**	Cl	Cl	CN	384	**2j**	77

[a] Reaction was carried out until **1** apparently disappeared on TLC.
[b] Isolated yield.
[c] The reaction was too slow to be continued.

As a consequence, for the synthesis of particular phenazine the most convenient way can be chosen. Phenazine **2f** could not be easily obtained from **1f** because the reaction was extremely slow (Table 1, entry 6). However, starting from isomeric nitrosoaniline **1g** the target phenazine can be obtained quickly and in high yield (entry 7). Similar considerations apply for other substituents with strong electronic effects.

In order to explain the differences in the reaction rates, a general mechanistic scheme of the reaction can be proposed (Scheme 1).

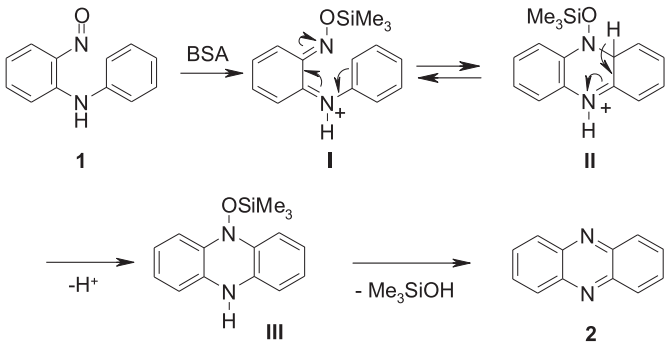
The electron rich oxygen atom of the nitroso group, additionally enriched by the *ortho*-amino group, is initially silylated by BSA to form first intermediate structure **I** comprising positively charged iminium group, an *ortho*-quinoid structure of the nitrosobenzene ring and a silylated oxime function. This reversible step is followed by irreversible aromatization of intermediate **II** and the reaction is concluded by elimination of trimethylsilanol.

Formation of **II** from **I** can also proceed in a reverse order, i.e. by reversible intramolecular addition of the nitrogen to the aryl ring followed by silylation of the oxygen atom.[15] While we could not distinguish these alternatives, further considerations based on the presented tentative scheme can be applicable essentially for both of them.

The main question is which step is the slowest, thus, responsible for the observed reaction rates. Attempts to isolate possible intermediates (**I**–**III** in Scheme 1) were unsuccessful. Thus, in order to answer this question the kinetic isotope effect (KIE) in the reaction of 2'-monodeuterated nitrosoaniline, in which the competitive cyclization at deuterated position 2′ and non-deuterated position 6′ occurs, was determined. The model 5-chloro-*N*-(2-deuterio-4-methoxyphenyl)-2-nitrosoaniline (**1h-*D***) was cyclized under standard conditions producing deuterated and non-deuterated phenazines **2e-*D*** and **2e** respectively (Scheme 2).

The obtained phenazine was found to be deuterated in 39% (by ^{1}H NMR). Taking into calculations a purity of starting **1h-*D*** the observed k_H/k_D = 0.91. The lack of primary isotope effect clearly indicates that the elimination step is not the rate-limiting step. Moreover, the observed k_H/k_D value may reflect secondary KIE caused by the change of the ring carbon atom hybridization from sp^2 to sp^3 during the addition step. Thus, the effect of substituents on the reaction rates can be attributed to their influence on the intramolecular addition step, and can be explained as follow (Fig. 1). Strong conjugation of the lone electron pair of X (structure **IV**) greatly reduces positive charge on the iminium nitrogen and consequently also electrophilicity of the *N*-aryl ring (structure **V**). Conversely, electron-withdrawing substituents X enhance reactivity of that ring while does not affect nucleophilicity of the oxime nitrogen atom, because of a lack of conjugation.

The opposite effect of the substituent Y, *para* to the amine



Scheme 1. Proposed mechanistic scheme for the formation of phenazines from *N*-aryl-2-nitrosoanilines in the presence of BSA.