Tetrahedron Letters 52 (2011) 6484–6488

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

N-Aryl-2-nitrosoanilines as intermediates in the synthesis of substituted phenazines from nitroarenes

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ARTICLE INFO

Article history:
Received 9 August 2011
Revised 14 September 2011
Accepted 23 September 2011
Available online 29 September 2011

Keywords:
Heterocycles
Nitroso group
Cyclization

ABSTRACT

N-Aryl-2-nitrosoanilines, available from the reaction of nitroarenes with anilide anions, undergo cyclization to furnish substituted phenazines. The reaction is promoted by potassium carbonate in methanol, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in aprotic solvents, and by acetic acid. The method is illustrated by the synthesis of 1-methoxyphenazine, a precursor of pyocyanine, starting from the appropriate nitroarene–aniline pairs.

Phenazines have been known since the nineteenth century. Many of them, initially isolated from natural sources and afterward obtained synthetically, exhibit significant biological activity, which, together with their biosynthesis, attract understandable attention.[1] There is continued interest in both developing new methods for the synthesis of phenazine derivatives and the design of potentially valuable analogs.

Numerous methods for the synthesis of substituted phenazines have been reported, however they have limitations, and are hence not considered as generally applicable.[2] In most cases, the crucial step in the synthesis of phenazines, particularly those that occur naturally, comprises the generation of their fused tricyclic skeleton by constructing the central heterocyclic ring. A popular approach is based on the preparation and cyclization of *ortho*-substituted diphenylamines. Reductive cyclization of *o*-nitro-,[3,4] *o*,*o*′-dinitro-,[5] and *o*-nitro-*o*′-fluorodiarylamines[4] has been reported, as well as oxidative cyclization of *o*,*o*′-diaminodiarylamines.[6] Promising results have been obtained using the intramolecular N-arylation of *o*-nitro-*o*′-bromodiarylamines catalyzed by Pd(0) complexes.[7] It should be stressed that the synthesis of appropriate diphenylamines as substrates in all the aforementioned methods is not always an easy task, especially when a specific substitution pattern in the target phenazine is required.

The condensation of *ortho*-benzoquinone derivatives, generated in situ from the corresponding catechols, with *o*-phenylenediamines, has for a long time been an important route leading directly to phenazines.[8,9] Benzoquinone derivatives, which are not readily available can be replaced with appropriate 1,2-diones which condense with 1,2-diaminoarenes, and after additional transformations lead to phenazines.[10] An adaptation of the Beirut reaction,[11] comprising dehydrative condensation of benzofuroxans with phenols leads to N,N-dioxides of phenazines. To provide the desired phenazines, a deoxygenation process is necessary. As the Beirut reaction suffers from incompatibility with several substituents, its scope is limited.

The Wohl–Aue reaction[12] is attractive as it consists of one-step, and involves an easy procedure starting from simple and available substrates, namely nitroarenes and anilines. However, this reaction has never found extensive application, due to its serious drawbacks. The reaction conditions are harsh and strongly basic, the yields are low to moderate and the phenazine products are accompanied by N-oxides and significant amounts of by-products. It is believed to proceed via addition of anilide anions to the *ortho*-position of the nitroarene followed by the formation of a 2-nitrosodiarylamine intermediate which cyclizes to form the final product.[12c] Concurrently, oxidation processes take place, which are responsible for the formation of the phenazine N-oxides and various products of reduction of the nitroarene, being mainly azo compounds.

The Wohl–Aue reaction sequence can be divided into two separate steps, carried out under different, more suitable conditions. Recently, we demonstrated that the reaction of nitroarenes with anilines, performed in the presence of excess potassium *tert*-butanolate in DMF or THF at low temperature, led to *N*-aryl-2-nitrosoanilines which could be isolated in good yields.[13] They were generally stable, easily handled compounds, which were found to be convenient starting materials for the synthesis of the corresponding *o*-phenylenediamines, *o*-nitroanilines and, particularly, polycyclic heterocycles.[13a,14] This sequence represents the first step of the above-mentioned two-step approach to phenazines.

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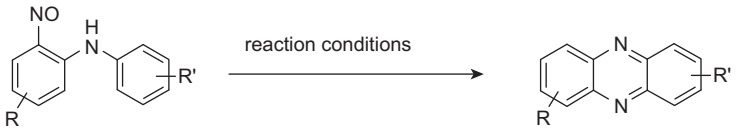
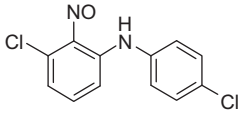
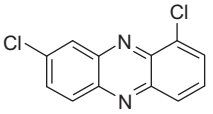
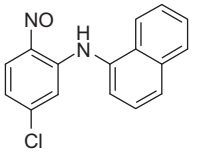
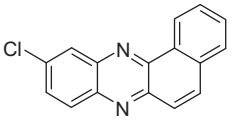
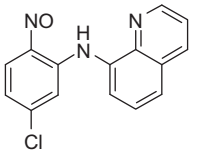
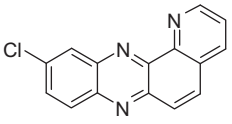
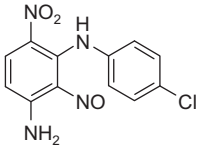
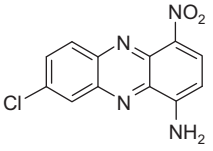
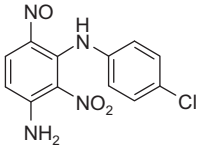
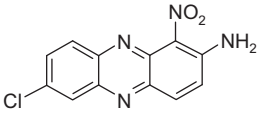
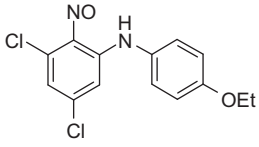
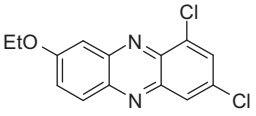
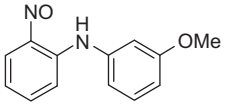
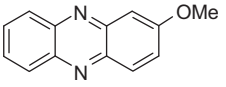
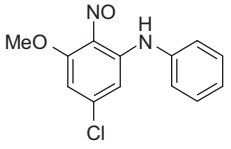
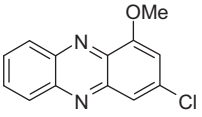
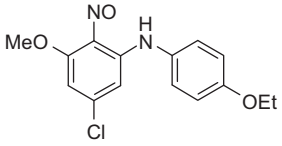
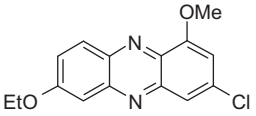
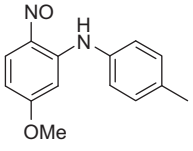
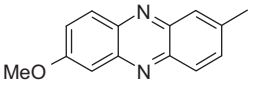
doi:10.1016/j.tetlet.2011.09.113

Table 1
Synthesis of phenazines **2a–n** from *N*-aryl-2-nitrozoanilines **1a–n**



Entry	Nitrosoaniline	Conditions	Temp	Time (h)	Phenazine	Yield (%)
1	 **1a**	K_2CO_3/MeOH	rt	3.5	 **2a**	84
2	 **1b**	K_2CO_3/MeOH	rt	1	 **2b**	67
3	 **1c**	K_2CO_3/MeOH	rt	1	 **2c**	78
4	 **1d**	AcOH	Reflux	1.5	 **2d**	97
5	 **1e**	AcOH	Reflux	1	 **2e**	93
6	 **1f**	AcOH	Reflux	3.5	 **2f**	69
7	 **1g**	AcOH	rt	2	 **2g**	68
8	 **1h**	BSA/DMF	rt	24	 **2h**	90
9	 **1i**	BSA/DMF	rt	24	 **2i**	99
10	 **1j**	BSA/MeCN	60 °C	24	 **2j**	99

(*continued on next page*)