



Synthesis of 4-(4-toluenesulfonyl)quinolines from nitroarenes and allyl sulfones using step-by-step procedure

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ABSTRACT

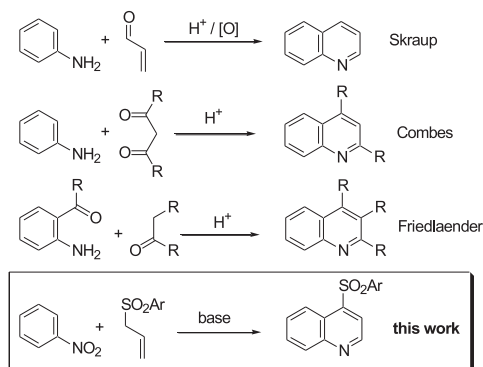
σ^H -Adducts formed from nitroarenes and allyl tolyl sulfone carbanions when treated with silylating agents transform into 4-toluenesulfonyl quinolines.

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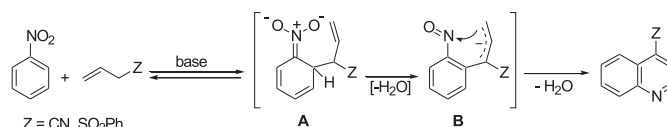
1. Introduction

Among the methods of synthesis of quinolines the most important are those dealing with the reaction of anilines with carbonyl compounds or their precursors, such as Skraup, Doebner–Miller, Combes, Conrad–Limpach, and Knorr reactions,¹ in which formation of the quinoline framework results from an electrophilic attack of a three-carbon atom system towards aniline, followed by cyclization and often by an oxidation of the intermediate formed dihydroquinoline (Scheme 1). These reactions are usually performed under strongly acidic conditions at elevated temperatures.

Much less widespread are methods employing reversed polarity of the reagents in which the electrophilic nitroarenes add nucleophilic three-carbon atom allyl carbanions to form quinolines or their *N*-oxides (Scheme 2).^{2–4} The σ^H -adducts (**A**) initially formed in these reactions transform into nitrosoarenes (**B**) according to an intramolecular redox stoichiometry. These processes can be considered as nucleophilic substitution of hydrogen in nitroarenes.^{5–10} Nitrosoarenes (**B**) bearing an allyl substituent *ortho* to the nitroso group undergo further cyclization by an intramolecular Ehrlich–Sachs condensation^{11,12} to form quinolines.



Scheme 1. Selected methods of synthesis of quinolines.



Scheme 2. Synthesis of quinolines from nitroarenes and allyl carbanions.

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reaction of cinnamyl tolyl sulfone with 1-nitronaphthalene in the presence of DBU and MgCl₂ in DMF led to 4-toluenesulfonylbenzo[h]quinoline in good yield.⁴ In this one-pot procedure good yields of quinolines (condensed pyridines) are obtained only with relatively highly electrophilic nitroarenes such as 1-nitronaphthalene, 5-nitroquinoline, 2-nitrothiophene, and 2-methoxy-5-nitropyridine. Less electrophilic nitrobenzene and its derivatives only reacted satisfactorily under these conditions with aryl cinnamyl sulfones to form 2-phenyl-4-arylsulfonylquinolines.³

This multistep process consists of a reversible formation of the σ^H -adduct, which then in reaction with a Lewis acid, eliminates water to form a nitroso compound. It should be noted that in some instances the nitrosoarenes arising from the σ^H -adducts are stable and can be isolated, for example, 2-nitrosodiphenylamines obtained in reaction of anilines with nitroarenes^{13,14} or alkyl nitrosoarenes obtained from alkylmagnesium reagents and bicyclic nitroarenes.¹⁵ The formation of the intermediate nitroso compounds is a crucial step in the synthesis of 2,1-benzisoxazoles (anthranils) from nitroarenes and phenylacetonitriles in protic media, for example, in the presence of NaOH in methanol (Davis reaction).¹⁶

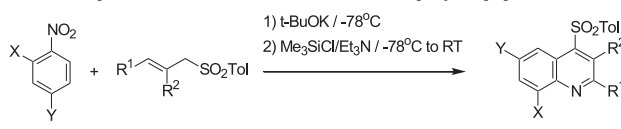
The effectiveness of additives supporting elimination of water from the σ^H -adduct varied depending on the reagents used: chlorotrimethylsilane as well as magnesium chloride or titanium tetraisopropoxide in the case of nitroarenes and cinnamyl sulfones, MgCl₂ for the intramolecular variant of the process, or mixtures of MgCl₂/BSA for some less reactive nitroarenes and allyl sulfones were used.⁴

In these 'one-pot' reactions the carbanion concentration is low due to application of a relatively weak base. For example, the pK_a of DBU-H⁺ was estimated to be ca. 12, and that of the cinnamyl phenyl sulfone was ca. 20.¹⁷ As a consequence, the concentration of the σ^H -adduct and the consecutively formed intermediates is low. However, attempts to use a stronger base like *t*-BuOK failed, probably due to its direct reaction with the Lewis acid or silylating agent. Another earlier observation was that low polar solvents (THF instead of DMF) facilitated formation of the σ^H -adduct *ortho* to the nitro group, thanks to its complexation to a cation of the approaching ion pair.¹⁸ It has been found that reactions of carbanions with nitroarenes at low temperature (–70 °C) results in complete formation of the σ^H -adducts.¹⁰ Following these observation we elaborated a 'step-by-step' procedure in which cooled (–70 °C) solution of nitroarene, carbanion precursor, and triethylamine in THF was treated with a solution of a strong base such as *t*-BuOK in THF. After some minutes, the reaction mixture was treated

nitrobenzene derivatives that did not react satisfactorily in the 'one-pot' reaction. Thus when 2-chloronitrobenzene (**1b**) and allyl tolyl sulfone (**2a**) in the presence of triethylamine were treated with *t*-BuOK at –78 °C, a brownish-green coloring appeared. After 10 min the reaction mixture was quenched with trimethylchlorosilane and allowed to reach room temperature. After work-up the expected 8-chloro-4-(4-tolylsulfonyl)quinoline (**3ba**) was obtained in 56% yield. Similarly other *ortho*-substituted nitrobenzene derivatives were treated with allyl sulfones (Table 1).

Table 1

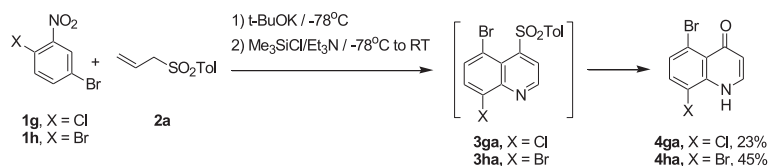
Formation of quinolines from nitrobenzenes via a 'step-by-step' procedure



Entry	Nitroarene 1		Sulfone 2		Quinoline 3			
	X	Y	R ¹	R ²		Yield (%)		
1	1a	F	H	2a	H	H	3aa	41
2	1b	Cl	H	2a	H	H	3ba	56
3	1c	Br	H	2a	H	H	3ca	48
4	1d	PhS	H	2a	H	H	3da	45
5	1e	Cl	Cl	2a	H	H	3ea	71
6	1e	Cl	Cl	2b	<i>t</i> -Bu	H	3eb	54
7	1e	Cl	Cl	2c	Me	H	3ec	50
8	1e	Cl	Cl	2d	H	Me	3ed	49
9	1f	Br	Cl	2a	H	H	3fa	61
10	1f	Br	Cl	2c	Me	H	3fc	48
11	1f	Br	Cl	2d	H	Me	3fd	52

The presence of a substituent *ortho*- to the nitro group seems to be crucial. In the absence of such a substituent only intractable mixtures of products were formed. 2,4-Dihalogenated nitroarenes **1e** and **1f** gave slightly better yields, probably due to their higher electrophilicity.

The 4-arylsulfonylquinolines **3ga** and **3ha** formed from 2,5-disubstituted nitroarenes **1g** and **1h** proved unstable, and during the aqueous work-up underwent fast replacement of the arene-sulfonyl group with water to form quinolin-4-ones **4ga** and **4ha** (Scheme 3). Such a reaction is facilitated by steric repulsion of the sulfonyl group and the substituent at the position 5. Earlier we observed replacement of the sulfonyl group in less hindered 4-sulfonyl quinolines with various nucleophiles.^{3,4}



Scheme 3. Synthesis of 5,8-disubstituted quinolin-4-ones.

with trimethylchlorosilane or pivaloyl chloride to give final product. This 'step-by-step' approach we successfully applied to synthesis of acridines from nitroarenes and benzyl carbanions and to synthesis of 3-aminoquinolines¹⁹ from nitroarenes and 3-aminocrotonates.²⁰

2. Results and discussion

Here we present the results of studies on the application of this 'step-by-step' procedure to synthesis of quinoline derivatives from nitroarenes and allylic sulfones. We were interested in reactions of

At first glance successful reactions only in nitrobenzenes bearing an *ortho*-substituent resembles that observed by Bartoli in the reactions of *ortho*-substituted nitroarenes with vinyl Grignard reagents furnishing indoles.²¹ This reaction was proved to proceed via an intermediate nitrosoarene arising from reduction of the nitro group with a vinyl Grignard reagent. This similarity turned out to be coincidental, and the mechanism of the formation of quinolines via reaction of an intermediate nitrosoarene was ruled out since no expected product was observed when *ortho*-bromonitrosobenzene was reacted with allyl tolyl sulfone under analogous conditions.

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