

Microwave enhanced greener synthesis of indazoles via nitrenes

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Dedicated to Richard Glazer

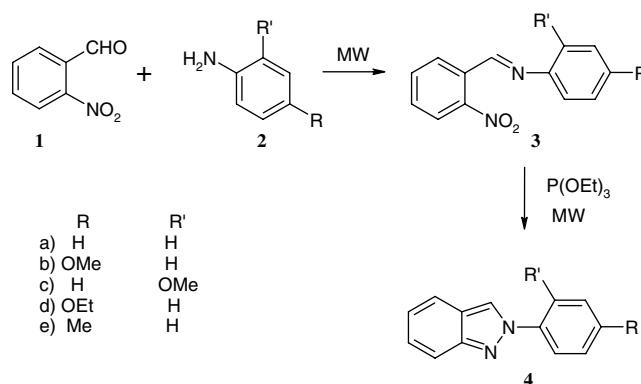
Abstract—Non-traditional methods (grinding, water-based biphasic reactions, microwave chemistry) were used for the preparation of Schiff bases from several amines and 2-nitrobenzaldehydes. These nitro compounds were allowed to react with triethyl phosphite under microwave irradiation for the generation of nitrenes that underwent insertion reactions to form indazoles. This procedure constitutes an energy-efficient, greener chemistry version of the Cadogan reaction for nitrene-based formation of nitrogen heterocycles.

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1. Introduction

Cadogan and co-workers published a series of papers starting in 1962 that described the synthesis of a variety of nitrogen containing heterocycles by the deoxygenation of aromatic nitro compounds; an excess of triethyl phosphite served as the reducing agent at high temperature under nitrogen; several hours of reaction time were required.¹ The reaction mechanism involves the formation of a nitrene that undergoes an insertion reaction to form another nitrogen containing ring. In the course of our studies on redesigning classical reactions by using Microwave-induced Organic Reaction Enhancement ('MORE') chemistry techniques,^{2–4} the Cadogan reaction was re-investigated.⁵

A detailed description of the synthesis of 2-phenylindazole (Scheme 1, 4:R=R'=H) is given in *Organic Syntheses* as described by Cadogan and Mackie and checked by Dauben et al.⁶ The first step was the preparation of a Schiff base from *o*-nitrobenzaldehyde and *p*-anisidine by heating under reflux for a period of 2 h; ethyl alcohol was used as the solvent. The second step was the reaction of the Schiff base with excess triethyl phosphite by refluxing for 8 h under an inert atmosphere followed by a long work-up procedure ending with recrystalliza-



Scheme 1.

tion of the crude product from alcohol. These steps have been greatly shortened and improved in our laboratory by using microwave chemistry. Described below are energy-efficient greener chemistry approaches that were developed for this purpose.

2. Preparation of Schiff bases

Three green chemistry methods were studied for preparing Schiff bases:

- (a) *Microwave assisted synthesis.* Easily available isopropyl alcohol (sold in drug stores as rubbing alcohol) is a convenient and inexpensive reaction

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medium for the preparation of Schiff bases. A solution of an aldehyde (**1**) and an amine (**2**) was exposed to microwave irradiation for 1 or 2 min; the Schiff base (**3**) that was formed in high yield crystallized out on cooling the reaction mixture. If either the aldehyde or the amine is a liquid, it may not be necessary to use a solvent.

- (b) *Grindstone chemistry: a friction activated synthesis.*⁷ Exothermic reactions can be conducted by grinding the reactants together for a few minutes without using any organic solvent; this method does not seem to be effective for endothermic reactions. Since Schiff base formation is an exothermic reaction, this approach was used for the preparation of several Schiff bases. This procedure is a slight modification of a method described by Toda et al.⁸

In a typical experiment, a mixture of equivalent amounts of an amine and an aldehyde (a total of 2–10 g) was placed in a mortar and ground with a pestle made of porcelain. The reaction mixture thickened in 2–5 min and the temperature went up by 5–10 °C.

After storage at room temperature for 10–20 min, the solid product was purified by crystallization from isopropyl alcohol to give the pure Schiff base.⁹

- (c) *Water-based biphasic reactions.* Recently a water-based method was developed in our laboratory for conducting exothermic reactions when the reactants are organic liquids.¹⁰ It is a convenient and effective green chemistry method—especially if the product is a solid that crystallizes out—usually in

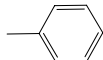
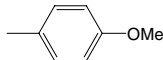
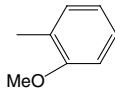
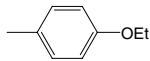
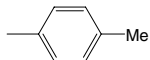
the pure form. This procedure is rapid and simple and the apparatus required is a container of an appropriate size and an electric stirrer. The method is suitable for small scale as well as multi-molar scale reactions.

For conducting a reaction by this method, a large amount of water (e.g., 1 L) is placed in the container and stirred. The reactants (e.g., several grams) are then added slowly to the water. In a few minutes, an exothermic reaction starts and the temperature of the mixture rises by 10–15 °C; cold water can be added to control this temperature rise. After a few more minutes, the solid product (Schiff base) begins to crystallize out in a nearly pure form—suitable as an intermediate for reactions without further purification. This method was found to be rapid, clean, and eco-friendly; the product was obtained in about 90% yield. Schiff bases in molar quantity were prepared by this convenient method (see Table 1).

3. Cadogan reaction: reduction with triethyl phosphite

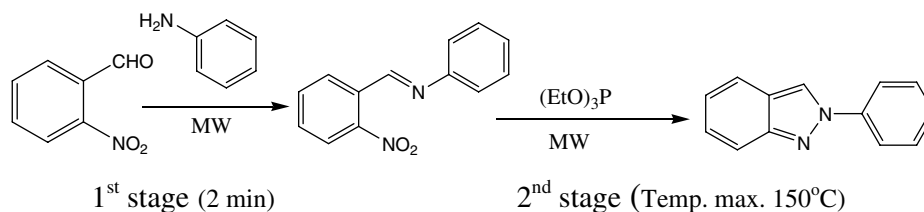
A pilot experiment was performed with the Schiff base derived from *o*-nitrobenzaldehyde **1** and *p*-anisidine **2b**. When this Schiff base **3b** was suspended in an excess of triethyl phosphite in a conical flask open to the atmosphere and irradiated for about 4 min at 1000 W in an unmodified domestic microwave oven, a yellow crystalline compound was obtained upon isolation and purification. From the melting point and spectral characteristics, this compound was identified as the target indazole **4b**; the yield was about 82%. It should be noted that an inert atmosphere recommended by Cadogan et al. was not employed (Scheme 1).

Table 1. Preparation of indazoles

Entry	Amine 2		Schiff base ^a 3 mp (°C)	Indazole ^b 4 Ar
	R	R'		
a	H	H	64–65	
b	OMe	H	84–85	
c	H	OMe	68–70	
d	OEt	H	86–87	
e	Me	H	129–130	

^a Yields for all Schiff base examples are about 90%.

^b Yields for indazoles ranged from 60% to 65%.



Scheme 2.

Excess triethyl phosphite was removed in early experiments by reaction with aqueous formaldehyde solution instead of distillation under reduced pressure as described by previous authors. A greener chemistry procedure was then sought that avoided reaction with formaldehyde.

Advantage was taken of the fact that triethyl phosphite is soluble in water. Conversion of triethyl phosphite to the corresponding phosphate was easily achieved in a few minutes by room temperature oxidation with 3% hydrogen peroxide. Washing with water removed the phosphates from the organic reaction mixture. The organic products were purified by crystallization from suitable solvents. Several indazoles were prepared on 0.5 g–2 g scale (Table 1) by this procedure in 60–70% yield based on the starting aldehyde.

3.1. One pot synthesis of indazoles

As an additional modification, we examined the possibility of forming the Schiff base in situ as an intermediate for the corresponding indazole. The two step Cadogan reaction for the synthesis of indazoles was subsequently modified and simplified to a one pot reaction under microwave irradiation (Scheme 2).

For example, a mixture of equivalent amounts of 2-nitrobenzaldehyde and aniline **2a** (Table 1) and an excess of triethyl phosphite was irradiated with microwaves for 10 min. For the first 2 min the power level was kept low (about 200 W), so that the temperature of the mixture was kept below 70 °C; then the temperature was allowed to rise to 150 °C by increasing the power to about 400 W (it should be noted that these parameters will depend on the particular microwave oven in use). The reaction was monitored by GC–MS. It was found that the reaction proceeds in two stages: the initial 2 min are the first stage that involves the formation of the Schiff base **3a** (Table 1), in the second stage cyclization to indazole **4a** (Table 1) occurs as the temperature is raised to about 150 °C.

3.2. Microwave equipment used

The experimental results reported in this letter were obtained a few years ago in the course of a carefully conducted Master's Thesis by Deepu J. Varughese entitled 'Microwave Assisted Nitrene Chemistry.'

The microwave equipment available at that time for synthetic work was the Milestone Microwave Labstation. A turntable was used for providing a reasonable

homogeneity of the field. Synthetic experiments conducted by us on a multiple gram scale (5–50 g) using this device gave essentially the same yields in repeated runs.

Acknowledgments

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9. For larger scale preparations, a glass or porcelain bowl of appropriate size and a hand-held electric (food) mixer with stainless steel rotors were used. It should be noted that the chemical reaction is exothermic; the temperature rise depends on the quantity of the material used and the exothermal nature of the reaction. The mixer was started at the lowest speed and then the speed was gradually increased to produce gentle but thorough mixing; the temperature rise was not allowed to exceed 20 °C above the room temperature. This method was found suitable even if one or both components were liquids but the Schiff base was a solid. If both components were liquid, coarsely crystalline Epsom salt (MgSO₄·7H₂O) or sand was added for increasing friction. If Epsom salt had been added, it was removed by adding water in which the salt is easily soluble. When sand was added instead of the Epsom salt, the organic product was extracted with an organic solvent, such as isopropyl alcohol or dichloromethane. The Schiff base was purified by crystallization from isopropyl alcohol or methanol.
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