

Bischler Indole Synthesis under Microwave Irradiation: A Solvent-Free Synthesis of 2-Arylindoles

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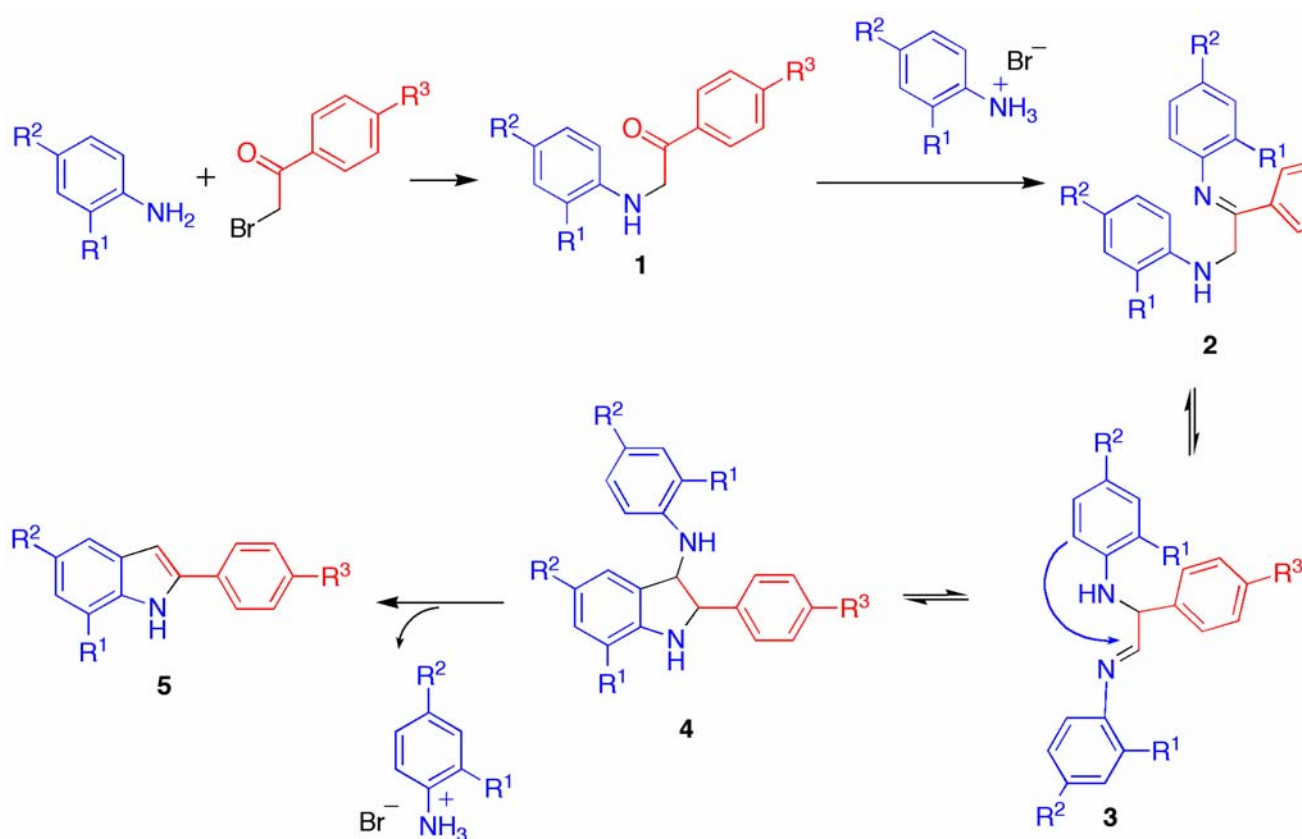
Abstract. - *The solid-state reaction between anilines and phenacyl bromides in the presence of an equimolecular amount of sodium bicarbonate gives phenacylanilines. Microwave irradiation of mixtures of these compounds with anilinium bromides at 560 W for 45-60 s provides a general, solvent-free method for the synthesis of 2-arylindoles in 50-56% overall yields. A one-pot variation of the method, involving irradiation of 2:1 mixtures of anilines and phenacyl bromides, allowed a simplified experimental procedure and led to improved yields (52-75%).*

Introduction

The development of solvent-free synthetic methods [2] is of considerable current interest because of the economical and environmental concerns associated with organic solvents. The synthesis of indoles is a very active field due to their widespread occurrence in nature and their wide-ranging biological activities. Besides the traditional procedures [3], modern emphasis is on methods that rely on the transition metal-catalyzed cyclization of o-alkynylanilines, although these procedures have the disadvantage of requiring one or several steps involving the use of stoichiometric amounts of metals to introduce the ortho side chain prior to the

cyclization, and also that they normally require a nitrogen protecting group. Some copper [7] or palladium [8]-catalyzed domino protocols are known for the transformation of N-protected 2-iodoanilines into indoles, without the need to isolate intermediate o-alkynyl intermediates, but the preparation of the starting materials from commercially available anilines is still necessary.

In this context, the traditional but relatively unexploited Bischler indole synthesis [3], based on an intramolecular electrophilic cyclization, appeared to us as ideally suited as a starting point for the development of a green indole synthesis, since it does not require the use of nitrogen protecting groups or metallic reagents or catalysts. The Bischler indole synthesis involves monoalkylation of anilines with phenacyl bromides to give compounds **1**, followed by treatment with an aniline hydrobromide, which forms an imine **2** by reaction with **1**. Because of the high temperatures required, which favour thermodynamic control, the more stable imine tautomer **3** predominates and its cyclization gives **4**, which then evolves to the final product **5** by loss of the initial aniline (Scheme 1). We describe in this communication a user-friendly, solvent-free protocol for the preparation of 2-arylindoles under Bischler conditions.



Scheme 1

Results and Discussion

Our first task was to develop a simple protocol that allowed the crucial monoalkylation of anilines with phenacyl bromides to give phenacylanilines **1** efficiently and under solvent-free conditions. We found that by simply mixing equimolecular amounts of both reagents and sodium bicarbonate and allowing the reaction to proceed in the solid state for 3 h at room temperature, compounds **1** were obtained in good to excellent yields and in adequate purities for the next stage.

Regarding the effect of microwave irradiation on the Bischler reaction, we discovered that irradiation at 540 W for 1 min of a slurry obtained by addition of 3 drops of dimethylformamide to a mixture of N-phenacylaniline and anilinium bromide led to 2-phenylindole in 71% yield (56% overall from aniline). Reaction of other compounds **1** with the suitable anilinium bromide led to several 2-arylindoles in good yields, as summarized in Table 1. A variety of substituents, both electron-withdrawing and electron-releasing, could be accommodated without significant differences in reaction time or yield. Besides the much milder conditions and shortened reaction times, our method also represents a considerable improvement in yield in those cases where the availability of literature data enables a comparison. For instance, the yield of 2-phenylindole (**5a**) is 17% under the conventional conditions [9].

Table 1

Compound	R ¹	R ²	R ³	Microwave irradiation time, s	Overall yield of
5a	H	H	H	60	56
5b	H	H	Cl	45	55
5c	H	H	CH ₃	60	51
5d	H	CH ₃	H	60	53
5e	H	Cl	H	45	54
5f	CH ₃	H	H	60	51
5g	H	CH ₃	CH ₃	45	50
5h	H	CH ₃	Cl	60	52
5i	OCH ₃	H	H	60	50

As a refinement of our method, we next developed conditions that allowed the transformation of anilines and phenacyl bromides into indoles in a single operation. Thus, when 2:1 mixtures of the suitable aniline and phenacyl bromide were stirred for 3 h and then irradiated for 1 min at 600 W in the presence of 3 drops of dimethylformamide but with no added sodium bicarbonate, the expected 2-arylindoles were obtained in one pot. As shown in Table 2, these reactions normally proceeded in improved yields with regard to the two-step method, and with the obvious advantage of a faster and more convenient operation.

Compound	R ¹	R ²	R ³	Yield, %
5a	H	H	H	75
5b	H	H	Cl	52
5c	H	H	CH ₃	54
5d	H	CH ₃	H	56
5e	H	Cl	H	59
5f	CH ₃	H	H	67
5g	H	CH ₃	CH ₃	57
5h	H	CH ₃	Cl	55
5i	OCH ₃	H	H	56

In conclusion, we describe a general, economical and environmentally friendly protocol for the preparation of 2-arylindoles from anilines under mild conditions, either in two steps or in one pot, using solvent-free reactions in both cases and affording much improved yields in comparison with the traditional conditions.

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References and notes

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