Microwave-Assisted, Solvent-Free Bischler Indole Synthesis

Vellaisamy Sridharan, Subbu Perumal,[1] Carmen Avendaño, J. Carlos Menéndez*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain
Fax +34(91)3941822; E-mail: josecm@farm.ucm.es

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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 *N*-phenacylanilines. Microwave irradiation of mixtures of these compounds with anilinium bromides at 540 W for 45–60 s provides a mild, general, and environmentally friendly 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, was also developed, allowing a simplified experimental procedure and leading to improved yields (52–75%).

Key words: indole synthesis, aniline monoalkylation, solvent-free synthesis, microwave-assisted synthesis

One of the main aims of green chemistry is the reduction of the use of organic solvents because of the economical and environmental concerns associated with them, and therefore the development of solvent-free synthetic methods[2] is of the utmost importance. We describe in this paper a user-friendly, solvent-free protocol for the synthesis of 2-arylindoles under Bischler conditions.

Indole derivatives are of great significance because of their occurrence in nature as part of the structure of a large number of alkaloids[3] and their wide-ranging biological avtivity,[4] and for this reason indole synthesis is a very active field.[5] Besides the traditional procedures based, among others, on the Fischer, Reissert and Madelung reactions,[6] modern emphasis is on methods that rely on the transition metal-catalyzed cyclization of *o*-alkynylanilines. From the point of view of synthetic efficiency, these methods have the disadvantage of requiring one or several steps[7] to introduce the *ortho* side chain prior to the cyclization, and also that they normally require a nitrogen protecting group, which adds two more steps to the indole preparations. Besides the lengthy sequences and the use of stoichiometric amounts of metals in the side chain introduction, another limitation of these methods from economical and environmental perspectives is the need for the use of toxic and expensive transition metal reagents or catalysts, normally palladium complexes[8,9] or copper(II) salts,[10] in the cyclization stage. The introduction of gold(III) salts as catalysts represented an improvement,[11] as they do not require nitrogen protection, but they are toxic, their cost is very high and they still require the use of organic solvents. Cyclizations mediated by metal alkoxides[12] and other bases[13] are also known, but they are obviously unsuitable for base-sensitive substrates. Reduction of the number of steps of these sequences has been recently achieved by the development of some copper-[14] or palladium[15]-catalyzed domino protocols 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.

Several known methods for indole synthesis have the advantage of avoiding the need to prepare *o*-substituted anilines, including the classical Fischer indole synthesis and the Sommelet rearrangement of arylsulfonium ions,[16] but the need to transform the starting aniline into an hydrazone or a *S*-anilinosulfonium derivative, respectively, renders them less attractive than alternative routes. The Bartoli indole synthesis,[17] which starts from nitrobenzene derivatives, also belongs to the group of methods that do not require the introduction of a substituent *ortho* to a nitrogen function prior to the construction of the indole system, although its scope is also rather limited because it only works well with 2-substituted nitrobenzenes and it requires the use of a large excess of Grignard reagents. On the other hand, the traditional but relatively unexploited Bischler indole synthesis,[6,18] 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 (or Bischler–Möhlau) indole synthesis involves monoalkylation of anilines with phenacyl bromides to compounds **1**, followed by treatment with an aniline hydrobromide as a catalyst, which forms an imine **2** by reaction with **1**. Because of the high temperatures required, which favor thermodynamic control, the more stable imine tautomer **3** predominates. Its cyclization gives **4**, which then evolves to the final product **5** by loss of the initial aniline; the tautomerization of **2** to **3** explains the apparent migration of the aryl group to the indole C-2 position (Scheme 1). If **1** is N-substituted, this tautomerism is not possible and 3-arylindoles are obtained;[19] recently, the development of LiBr-mediated cyclization conditions has allowed the synthesis of N-unsubstituted 3-arylindoles from intermediates **1** containing several electron-releasing groups in the benzene ring that acts as the nucleophile.[20] Variations of the Bischler synthesis that allow the preparation of 2,3-unsubstituted indoles by cyclization of acetals are known,[21] although they are of limited scope regarding the type of substituents allowed on the benzene ring.

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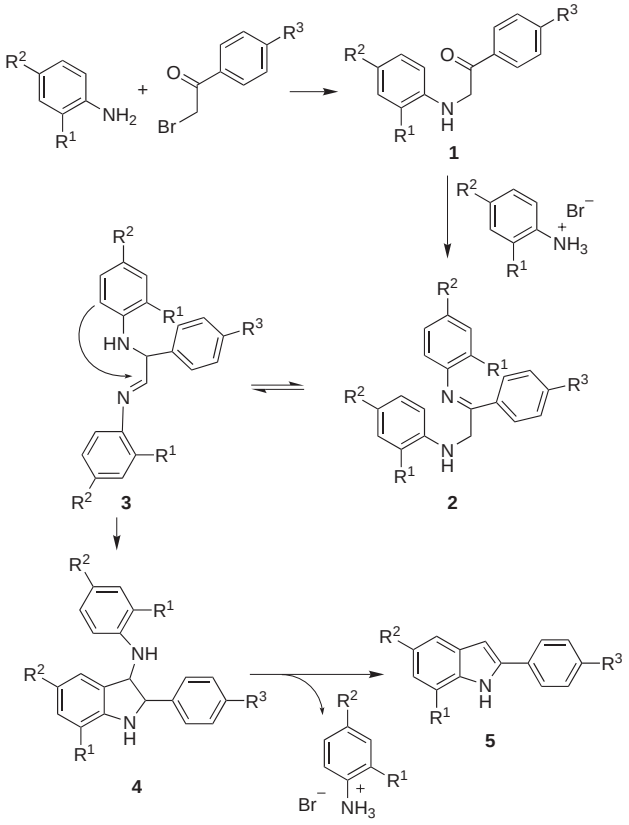

Scheme 1

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 three hours at room temperature, followed by washing with water, compounds **1** were obtained in good yields and adequate purities for the next stage. The cyclization step of the Bischler synthesis has been previously carried out under thermal conditions, by heating mixtures of phenacylanilines and the suitable aniline hydrobromide at 200–250 °C[22] or in a high-boiling solvent, like silicone oil,[23] and therefore we explored the possibility of improving this reaction by microwave irradiation, and particularly in the absence of solvent. Microwave irradiation[24] has long been considered as a green technology because it often allows solvent-free reactions and its level of energy consumption is low compared with more traditional methods. Our initial experiments involved *N*-phenacylaniline and anilinium bromide and, although they were encouraging in that the desired 2-phenylindole was isolated, the conversions were invariably low, even using reaction times of up to six minutes, and forcing conditions led to decomposition. Fortunately, after some experimentation, we eventually found that addition of three drops of dimethylformamide to the mixture of *N*-phenacylaniline and anilinium bromide prior to its irradiation at 540 watts for one minute allowed the isolation of 2-phenylindole in 71% yield (56% overall from aniline). This effect of dimethylformamide is probably due to its role as an energy transfer agent, related to its high dipole moment and leading to an increased reaction temperature,[25] although it is interesting to note that some attempts to carry out the reaction in an alumina bath in order to obtain high temperatures upon microwave irradiation were much less effective. In spite of the very short reaction times employed, the isolation of a 2-arylindole suggested that the same thermodynamic mechanism summarized in Scheme 1 was in operation under our microwave-enhanced conditions. Reaction of the remaining compounds **1** and the suitable anilinium hydrobromide (i.e. the hydrobromide of the aniline used for preparing **1**) led to isolation of 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.[26] 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.[27]

The literature contains at least one example where anilinium bromide was employed for catalyzing a Bischler reaction where the starting compound **1** came from a different, more nucleophilic aniline derivative, namely 3,5-dimethoxyaniline,[35] and it can be assumed that in this case the reaction was catalyzed by the 3,5-dimethoxyaniline liberated in the last step. Since the possibility of using the cheaper anilinium bromide at least for some cases was attractive, we attempted to perform the reaction leading to **4i** this way, but in our case the reaction product consisted of a 1:1 mixture of **4a** and **4i**, showing that competition between aniline and 2-methoxyaniline had taken place and that therefore this procedure must be assumed to be possible only when very activated anilines are liberated in the course of the reaction.

As a refinement of our method, we next sought to carry out the transformation of anilines and phenacyl bromides into indoles in a single operation. When 2:1 mixtures of the suitable aniline and phenacyl bromide were stirred for three hours and then irradiated for one minute at 600 watts in the presence of three 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.[36]

In conclusion, we describe a general, economically 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.

Table 1 Overall Yields for the Two-Step, Solvent-Free Bischler Indole Synthesis and Characterization Data of 2-Arylindoles Obtained

Compd	R^1	R^2	R^3	Microwave irradiation time (s)	Overall yield of **5** (%)	Mp of **5** (°C)
5a	H	H	H	60	56	190–191 (lit. 189.5–190)[28]
5b	H	H	Cl	45	55	207–208 (lit. 206–207)[28]
5c	H	H	CH_3	60	51	220–221 (lit. 220.5–221)[28]
5d	H	CH_3	H	60	53	220–221 (lit. 218–219)[29]
5e	H	Cl	H	45	54	200–201 (lit. 197–198)[30]
5f	CH_3	H	H	60	51	118–119 (lit. 117–118)[31]
5g	H	CH_3	CH_3	45	50	238–239 (lit. 239–240)[32]
5h	H	CH_3	Cl	60	52	252–253 (lit. 250.5–251.5)[33]
5i	OCH_3	H	H	60	50	85–86 (lit. 82–85)[34]

Table 2 Yields Obtained in the One-Pot Bischler Synthesis of 2-Arylindoles from 2:1 Mixtures of Anilines and Phenacyl Bromides

Compd	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

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(26) (a) **General Procedure for the Two-Step Method. N-Alkylation**: 2 mmol of the suitable phenacyl bromide (prepared according ref. 26b) was slowly added to a mixture of 2 mmol of the suitable arylamine and 300 mg of $NaHCO_3$ (the order of addition of the reagents is not normally of consequence, but it is important to use the method described here in the case of the anisidine derivatives, which otherwise lead to dialkylation products). The reaction mixture was stirred at r.t. with occasional cooling in tap water, soon becoming semisolid and finally solid. This solid was kept at r.t. for 3 h, when completion of the reaction was verified by TLC. Then, H_2O was added to the mixture and the separated solid was filtered, washed with H_2O, and dried, giving materials with sufficient purity for the next step. If desired, the *N*-phenacylanilines can be recrystallized from EtOH. **Cyclization**: a mixture of 1 mmol of the suitable *N*-phenacylaniline and 1.5 mmol of the corresponding anilinium hydrobromide with 3–4 drops of DMF was irradiated in a domestic microwave oven at 540 W for the time period specified in Table 1. After completion of the reaction the mixture was loaded onto a silica gel column and pure 2-arylindoles were obtained by chromatography, eluting with a gradient starting from 9:1 PE–EtOAc. Alternatively, the mixture could also be extracted with EtOAc, washed with H_2O, dried and evaporated before chromatography. All indole derivatives were previously known, and showed the expected ^1H NMR and ^{13}C NMR spectra, and melting points very similar to those previously described (Table 1). (b) Cowper, R. M.; Davidson, L. H. *Org. Synth. Coll. Vol. 2*; Wiley: New York, **1962**, 480.
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(36) **General Procedure for the One-Pot Synthesis of 2-Arylindoles from Phenacyl Bromides and Anilines under Microwave Irradiation.**
Phenacyl bromide (1 mmol) was stirred with aniline (2 mmol) at r.t. without any base to neutralize the liberated HBr. The mixture was kept at r.t. with occasional stirring for 3 h. To the solid mixture, containing *N*-phenacyl aniline and anilinium hydrobromide, was added 3–4 drops of DMF and the mixture was irradiated in a microwave oven at 600 W for 1 min. After completion of the reaction, the mixture was treated as described for the two-step method to give the pure 2-arylindoles.