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PTSA-Catalyzed Reaction of Indoles with 2-Oxoaldehydes: Synthesis of α,α-Bis(indol-3-yl) Ketones

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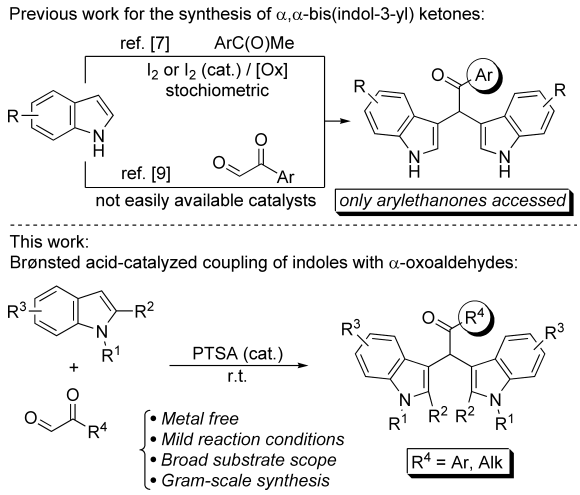
A convenient procedure for accessing α,α-bis(indol-3-yl) ketones from indoles and α-oxoaldehydes is described using an inexpensive and commercially available catalyst such as *p*-toluenesulfonic acid monohydrate. This protocol allows for the first time the synthesis of 2,2-bis(indolyl)-1-alkylethanones by employing aliphatic 2-oxoaldehydes, even as aqueous solutions. The high-yielded obtained ketones have been shown as useful starting materials for further synthetic transformations.

Introduction

The development of methods to construct C-C bonds in a selective and efficient way to generate functionalized molecules, with the production of the minimum amount of wastes, is a key goal of modern chemistry research. In the context of arene chemistry, Friedel-Crafts alkylation is one of the most important C-C bond-forming reactions, usually catalyzed or mediated by protic or σ-Lewis acid species.[1] In this field, the (hetero)arylation reactions of carbonyl compounds have been thoroughly studied.[2] Starting from indoles and carbonyls, 3,3 '-bis(indolyl)methanes[3] have been prepared assisted by a variety of Lewis or Brønsted acids.[4] These scaffolds are important indole derivatives that occur naturally in some vegetables and exhibit a range of important biological activities,[5] and have also been used in materials science.[6] Their unique properties have generated a growing interest in accessing to different functionalized 3,3'-bis(indolyl)methanes.[3–6] Particularly attractive is the presence of functional groups that acting as versatile building blocks, like the carbonyl group, facilitate the syntheses of libraries of compounds. Despite of their potential, few methods for the synthesis of α,α-bis(indol-3-yl) ketones have been established and all of them are restricted to 2,2-bis(indol-3-yl)-1-arylethanones. One of the disclosed approaches involves the reaction of indoles with aryl methyl ketones, and styrenes or α-hydroxyacetophenones, using I_2/DMSO or SeO_2 as external stoichiometric oxidants (Scheme 1).[7] In accordance with the developed strategies for the preparation of bis(indolyl)methanes, the most direct access to α,α-bis(indol-3-yl) ketones would be the reaction of indoles with α-oxoaldehydes. However, very few reports have appeared in the literature regarding the reaction of indoles with arylglyoxals for accessing these ketones.[8] The only two described catalytic methodologies involve the use of non easily available catalysts such as boron sulfonic acid or Ag nanoparticles (Scheme 1).[9] In addition, no examples with α-oxoaldehydes apart from arylglyoxals have been reported.[10] Therefore, the development of robust, yet practical, synthetic methods for preparing α,α-bis(indol-3-yl) ketones remains an important goal in this field. An ideal procedure should possess high functional group tolerance, avoid the use of precious metals-derived catalysts as well as hazardous/toxic reagents, do not generate side products and, as far as possible, provide the desired product and save having to further purify it. Herein, we report a new access to this bis(indolyl)methane derivatives by using a commercially and easily available Brønsted acid catalyst (Scheme 1).



Scheme 1. Methods for the synthesis of α,α-bis(indol-3-yl) ketones.

Results and Discussion

Based on our previous experience in the direct nucleophilic substitution of alcohols with indoles catalyzed by simple

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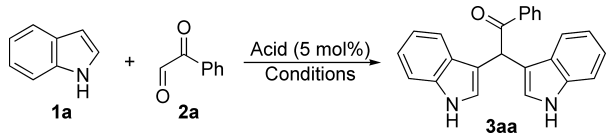
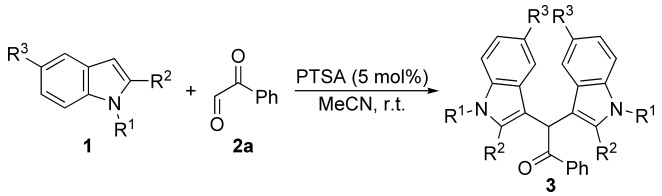
Table 1. Optimization studies of the reaction conditions for the synthesis of α,α-bis(indol-3-yl) acetophenone **3aa.**[a]



Entry	Acid	Solvent	T (°C)	t (h)	Yield [%][b]
1	PTSA	MeCN	20	1	98
2	PTSA	CH_2Cl_2	20	3	95
3	PTSA	Toluene	20	3	94
4	-	MeCN	20	48	<5
5	-	H_2O	80	48	<5
6	-	CF_3CH_2OH	20	48	<10
7	CSA[c]	MeCN	20	1	98
8	DNBSA[d]	MeCN	20	1	93
9	PS-PTSA[e]	MeCN	20	5	97

[a] All reactions were performed with 1 mmol of the corresponding indole **1a** and 0.5 mmol of phenylglyoxal **2a** in the corresponding solvent (0.5 mL). [b] Isolated yield based on the starting indole. [c] (+)-10-Camphorsulfonic acid. [d] 2,4-Dinitrobenzenesulfonic acid. [e] Polymer-supported *p*-toluenesulfonic acid.

Table 2. Scope of the PTSA-catalyzed coupling of indoles **1** with phenylglyoxal **2a.**[a]



Entry	Indole	R^1	R^2	R^3	Product	Yield [%][b]
1	**1b**	Me	H	H	**3ba**	99
2	**1c**	Me	Me	H	**3ca**	95
3	**1d**	Me	Ph	H	**3da**	99
4	**1e**	H	Me	H	**3ea**	98
5	**1f**	H	Ph	H	**3fa**	99
6	**1g**	H	H	Br	**3ga**	85
7	**1h**	H	H	CO_2Me	**3ha**	99
8	**1i**	H	H	NO_2	**3ia**	75

[a] All reactions were performed with 2 mmol of the corresponding indole **1** and 1 mmol of phenylglyoxal **2a** in MeCN (1 mL). [b] Isolated yield based on the starting indole.

Brønsted acids such as PTSA[11] we envisioned that this protic acid could also catalyze the reaction of indoles with α-oxoaldehydes. We selected indole **1a** and phenylglyoxal **2a** as model substrates to assess the viability of the desired Friedel-Crafts alkylation (Table 1). The initial experiment conducted in MeCN at room temperature showed complete conversion in a short reaction time allowing the isolation of α,α-bis(indol-3-yl) acetophenone **3aa** in almost quantitative yield by simple filtration (entry 1). Further tests, performed in other solvents (entries 2 and 3) led to no improvements in yield or reaction time. The role of the catalyst turned out to be crucial as demonstrated in a parallel reaction in MeCN without PTSA (entry 4), although a related process has been previously reported to proceed in high yield.[12] We also checked that other catalyst-free procedures, which have been recently described for the dehydrative S_N1-type reaction of indol-3-yl methanols,[13] do not work for the proposed transformation (entries 5 and 6). Next, the influence of the Brønsted acid catalyst was briefly examined. Other commercially available sulfonic acids such as camphorsulfonic acid (CSA) and 2,4-dinitrobenzenesulfonic acid (DNBSA) also worked as active catalysts for this transformation giving also rise to high yields of **3aa** (entries 7 and 8). In addition, this reaction could also be carried out using commercially available polymer-bound PTSA as catalyst, although an increased reaction time was needed (entry 9). The recovered polymer displayed similar catalytic activity in a subsequent experiment, showing the possibility of reusing it.

With the optimized conditions in hand (Table 1, entry 1), we decided to explore the generality of this method. First the indole moiety was modified keeping phenylglyoxal **2a** as α-oxoaldehyde partner (Table 2). More nucleophilic *N*-methylindole **1b** performs similarly to model indole **1a** (entry 1). Also, almost quantitative yields were obtained when 2-alkyl or 2-aryl substituted indoles **1c-1f** were investigated under the standard conditions (entries 2-5). Remarkably, the reaction proceeds smoothly leading to high yields, even with more challenging indoles **1g-1i** bearing moderate (entry 6) to strong electron-withdrawing groups (entries 7 and 8).

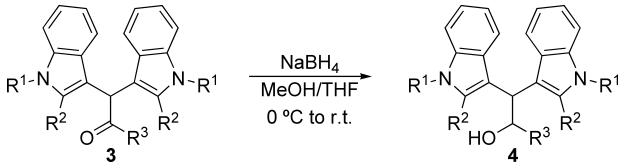
Once we had demonstrated the viability of different indoles **1** as nucleophiles, the scope of the process regarding the α-oxoaldehyde counterpart **2** was explored (Table 3). So, 1*H*-indole **1a** was treated with a variety of functionalized arylglyoxals **2b–e**, bearing both electron-donating and electron-withdrawing groups, under the standard conditions, leading to the corresponding bis(indolyl) derivatives **3ab-3ae** in high yields (entries 1-4). To the best of our knowledge, alkylglyoxals have never been used for these bis(heteroarylation) reactions with indoles, so we decided to test our methodology by using the commercially available aqueous solution of pyruvic aldehyde (**2f**) as 2-oxoaldehyde counterpart. Gratifyingly, its treatment with a selection of indoles **1a–c** gave rise to the corresponding α,α-bis(indol-3-yl)acetones **3af-3cf** (entries 5-7) and no deleterious effect due to the presence of

Table 3. Scope of the PTSA-catalyzed coupling of indoles **1** with α-oxoaldehydes **2.**[a]

Entry	Indole	R^1	R^2	**2**	R^3	Product	Yield [%][b]
1	**1a**	H	H	**2b**	4-$MeOC_6H_4$	**3ab**	96
2	**1a**	H	H	**2c**	3,4-$(CH_2)O_2C_6H_3$	**3ac**	95
3	**1a**	H	H	**2d**	4-FC_6H_4	**3ad**	80
4	**1a**	H	H	**2e**	4-$NO_2C_6H_4$	**3ae**	60
5	**1a**	H	H	**2f**	Me	**3af**	95
6	**1b**	Me	H	**2f**	Me	**3bf**	88
7	**1c**	Me	Me	**2f**	Me	**3cf**	99
8	**1a**	H	H	**2g**	*c*-C_6H_{11}	**3ag**	82
9	**1b**	Me	H	**2g**	*c*-C_6H_{11}	**3bg**	70
10	**1a**	H	H	**2h**	*t*-Bu	**3ah**	79
11	**1b**	Me	H	**2h**	*t*-Bu	**3bh**	72

[a] All reactions were performed with 2 mmol of the indole **1** and 1 mmol of α-oxoaldehyde **2** in MeCN (1 mL). [b] Isolated yield based on the starting indole.

Table 4. Synthesis of tryptophol derivatives **4.**[a]



Entry	**3**	R^1	R^2	R^3	Product	Yield [%][b]
1	**3aa**	H	H	Ph	**4aa**	97
2	**3ba**	Me	H	Ph	**4ba**	89
3	**3ca**	Me	Me	Me	**4ca**	99
4	**3ea**	H	Me	Ph	**4ea**	88
5	**3cf**	Me	Me	Me	**4cf**	96

[a] All reactions were performed with 2 mmol of the α,α-bis(indol-3-yl) ketone **3** in MeOH/THF (3/2) (4 mL). [b] Isolated yield based on the starting ketone.

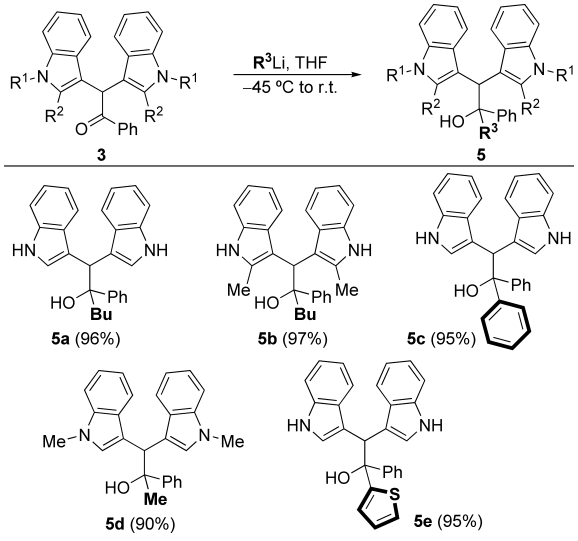
higher amounts of water was observed. Next other 2-oxoaldehydes bearing different alkyl substituents were also examined; it was found that secondary and tertiary alkyl groups are well tolerated accessing to 1-alkyl-2,2-bisindolylethanones **3ag-3bh** in high yields (entries 8-11).

The water and air tolerance combined with the simplicity of this protocol that uses inexpensive and easily accessible PTSA as catalyst is amenable to scale up. Several gram-scale reactions were performed to test its scalability accessing to gram amounts of compounds **3aa** (3.90 g, 99%), **3ba** (1.75 g, 99%), **3ca** (1.90 g, 96%) and **3ea** (1.81 g, 97%).

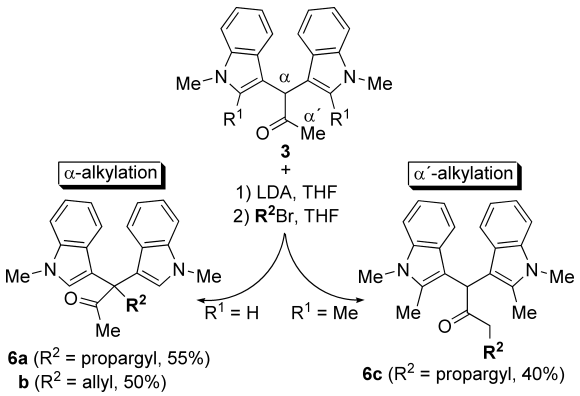
With gram-amounts of α,α-bis(indol-3-yl) ketones **3** in hand, several derivatives were easily constructed illustrating the versatility of the carbonyl ketone moiety. For example simple $NaBH_4$ mediated reduction of the ketone to secondary alcohol provides access to valuable tryptophol[14] scaffolds (Table 4). Additionally streptindole or arsindoline B derivatives could be easily obtained reaction if further manipulations through esterification of alcohols **4** are performed leading to the correlated acetates or propanoates esters.[15]

Furthermore, ketones **3** could also undergo nucleophilic addition reactions leading to alternative tryptophol derivatives. When α,α-bis(indol-3-yl) ketones **3** were treated with alkyl, aryl or heteroaryl organolithium reagents, tertiary alcohols **5** were obtained in excellent yields (Scheme 2).

Also C-C bond forming reactions involving C-alkylation on α position of ketones **3** could be easily accomplished (Scheme 3). Preliminary results show complete control on the regioselectiviy of the process, which seems to depend on the nature of the starting material. So, when using ketone **3bf**, with no substituent at C-2 of the indole nucleus, alkylation is completely favored on the methyne position α attached to both indoles that bears the more acidic proton generating functionalized ketones **6a,b.** On the other hand, when sterical hindrance around this site is increased due the presence of substituents on position 2 of



Scheme 2. Synthesis of tertiary alcohols **5.**



Scheme 3. Synthesis of ketone derivatives **6.**

the indole moieties, like in ketone **3 cf**, C-alkylation takes place selectively on most accessible α′ position leading to ketone **6 c** in moderate yields (Scheme 3).

Conclusions

A scalable straightforward robust methodology to synthesize α,α-bis(indol-3-yl) ketones from indoles and 2-oxoaldehydes has been described. This procedure is based on the use of inexpensive and widely accessible PTSA as catalyst. The superior conditions disclosed also enable the unprecedented use of alkylglyoxals as reaction partners, providing access to more elusive 1-alkyl-2,2-bis(indolyl)ethanones. Moreover, the versatility of ketone group as building block was illustrated by diverse derivatization reactions.

Supporting Information

Full experimental details, characterization data for all compounds, and copies of NMR spectra are available in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Brønsted acids · indoles · ketones · 2-oxoaldehydes · synthetic methods

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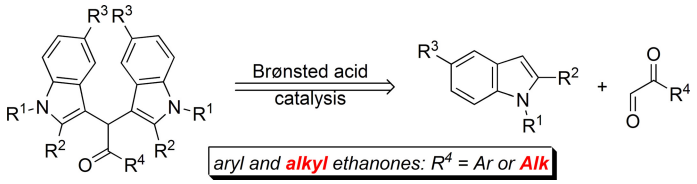

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A general and scalable method for synthesizing α,α-bis(indol-3-yl) ketones has been developed from indoles and 2-oxoaldehydes using easily available PTSA as Brønsted acid catalyst. Elusive 1-alkyl-2,2-bis(indolyl) ethanones have been also prepared from alkyl glyoxals. A wide variety of functionalized tryptophol derivatives has been accessed showing the synthetic potential of the obtained ketones.