Gold-Catalyzed Synthesis of 2-Substituted, 2,3-Disubstituted and 1,2,3-Trisubstituted Indoles in [bmim]BF_4

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Received 1 March 2007

Abstract: Cyclization of 2-alkynylanilines in the presence of $NaAuCl_4\cdot H_2O$ using [bmim]BF_4 as the reaction medium afforded 2-substituted indoles in high yields. The catalyst system was best recycled using *n*-Bu_4NAuCl_4. 2,3-Disubstituted indoles could be prepared from 2-alkynylanilines and 3-buten-2-one through a one-flask annulation–alkylation sequence and 1,2,3-trisubstituted indoles were obtained from the same starting materials via an aza-Michael addition–annulation–alkylation process.

Key words: gold catalysis, ionic liquids, indoles, hydroamination, aza-Michael addition

The development of new, efficient, clean and selective synthetic methods for the preparation of indole derivatives is the target of many current studies[1] due to their central role as versatile building blocks in the synthesis of natural products and in the design of therapeutic agents.[2] Increasing attention is now being paid to simplification and improvement of the existing procedures for their preparation in the manufacture of pharmaceutical targets. In this context, some of the main research areas involve the construction of the indole ring system from acyclic precursors[3] and the development of cheap and environmentally safe protocols.[4]

As a response to legislative and social pressure and 'green'-conscious industrial community, researchers have started to examine more eco-friendly and sustainable chemical processes. Toxicity and recycling considerations are influencing the choice of solvents and reagents to use.

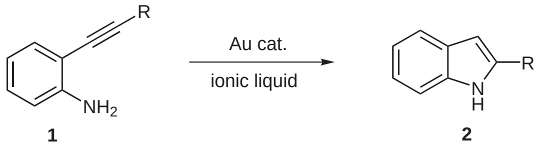
Ionic liquids[5] represent a class of alternative solvents which are currently receiving serious consideration because of their environmental and technological benefits.[6] The development of reactions in ionic liquids is not only important on the laboratory scale but also for industrial applications.[7] Moreover, ionic liquids can accomplish control of product distribution, enhanced reaction rate and/or reactivity, ease of product recovery, catalyst immobilization and recycling.

Among the various synthetic strategies, catalytic transformations by using transition metals is one of the most investigated approaches for assembling indole rings.[8] In particular gold catalysis[9] has been proven to be very effective to promote their preparation via annulation of 2-alkynylaniline derivatives **1**.[3a,10] The reaction can be carried out in ethanol or ethanol–water mixtures[10a] in good yields. Although environmentally benign, these reaction media do not allow catalyst/solvent recycling. Therefore, combining a gold-catalyzed annulation of **1** with recycling the catalytic system would be of great importance for large-scale production of these derivatives.

To the best of our knowledge, there are rare reports on reusable gold catalysts (immobilized complexes),[11] though gold-catalyzed reactions have become a hot topic in organic synthesis. The extensive use of *n*-$Bu_4N[AuCl]_4$ in [bmim]BF_4 ([bmim]$^+$ stands for the 1-butyl-3-methylimidazolium cation) as substitute for molecular solvents in catalytic reactions in recent years[12] turned out to be advantageous in the cyclization of 2-(1-alkynyl)-2-alken-1-ones to form highly substituted furans, because of the ready availability and recyclability of [bmim]BF_4.[13]

With the aim of developing a synthetic protocol involving the use of more environmentally benign solvents and avoiding the need of protecting groups[14] and/or harsh conditions, we decided to investigate the gold-catalyzed annulation of 2-ethynylaniline derivatives to 2-substituted indoles **2** in ionic liquids (Scheme 1).

Herein, we wish to report the preliminary results of our investigation. 2-(Phenylethynyl)aniline (**1a**; R = Ph) was selected as the model substrate in imidazolium salts.



Scheme 1

The more representative results of this investigation are reported in Table 1. As shown by these results, treatment of **1a** with a variety of gold catalysts in [bmim]PF_6 and [bmim]BF_4[15] at 50 °C led to indoles in a very simple fashion. However, when [bmim]Cl was used as the reaction medium, the reaction failed to give detectable amounts of **2a** (entry 5). Almost the same high yields of **2a** were obtained by using commercially available $NaAuCl_4\cdot 2H_2O$

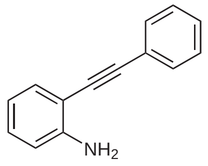
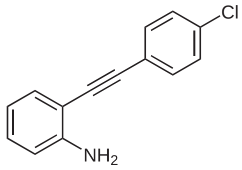
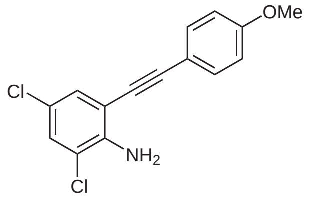
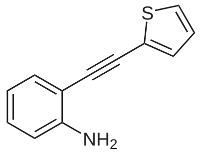
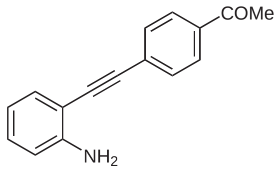
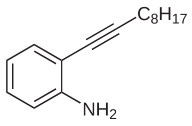
SYNLETT 2007, No. 11, pp 1775–1779
Advanced online publication: 25.06.2007
DOI: 10.1055/s-2007-982572; Art ID: Y00807ST

Table 1 Gold-Catalyzed Cyclization of **1a** to **2a**[a] in Ionic Liquids

Entry	Catalyst	Ionic Liquid	Yield of **2a** (%)[b]
1	[bmim]$AuCl_4$	[bmim]BF_4	92
2	*n*-Bu_4NAuCl_4	[bmim]BF_4	91
3	$NaAuCl_4{\cdot}2H_2O$	[bmim]BF_4	92
4	$NaAuCl_4{\cdot}2H_2O$	[bmim]PF_6	92
5	$NaAuCl_4{\cdot}2H_2O$	[bmim]Cl	0[c]

[a] Reactions were carried out on a 0.26-mmol scale with catalyst (0.0026 mmol) in solvent (1.0 mL) at 50 °C for 24 h.
[b] Yields are given for isolated products.
[c] **1a** was recovered in quantitative yield.

Table 2 Gold-Catalyzed Synthesis of 2-Substituted Indoles **2** from 2-Alkynylanilines **1**[a]

Entry	2-Alkynylaniline **1**	Indole **2** Yield (%)[b]
1	 **1a**	**2a** (91)
2	 **1b**	**2b** (94)
3	 **1c**	**2c** (95)
4	 **1d**	**2d** (92)
5	 **1e**	**2e** (94)
6	 **1f**	**2f** (92)

[a] Reactions were carried out on a 0.26-mmol scale in [bmim]BF_4 (1.0 mL) at 50 °C for 24 h using the following molar ratio: **1**/$NaAuCl_4{\cdot}2H_2O$ = 1:0.01.
[b] Yields refer to single runs and are for pure isolated products.

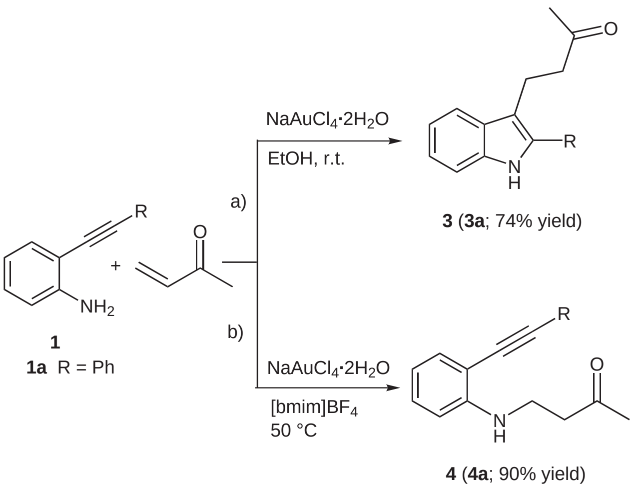
and *n*-Bu_4NAuCl_4 or [bmim]$AuCl_4$, prepared from [bmim]Cl and $NaAuCl_4{\cdot}H_2O$.[16]

Subsequently, the $NaAuCl_4{\cdot}2H_2O$-based protocol in [bmim]BF_4 was extended to alkynylanilines **1b**–**f** and the corresponding indoles were isolated in high yields[17] (Table 2). Experimentally, the isolation of products is simple. They were selectively and quantitatively extracted from [bmim]BF_4 solutions by several extractions with small portions of diethyl ether. In every case, the use of [bmim]BF_4 resulted to be superior to that of molecular solvents.[10a] The corresponding indoles were isolated in higher yields in all comparisons. In addition, a lower catalyst loading was always used. Under these conditions, the advantages of ionic liquids over molecular solvents are even more evident. For example, **1e** was cyclized in 94% yield using 1 mol% of catalyst in [bmim]BF_4 (entry 5) whereas utilization of EtOH (all other parameters remaining unchanged) led to the isolation of **2e** in only 69% yield.

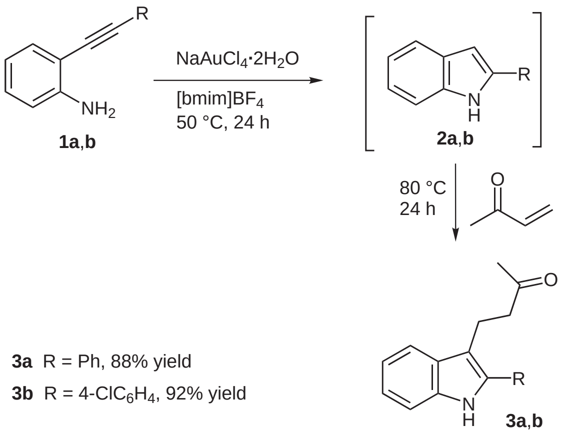
The alkynylanilines could also be cyclized under solvent-free conditions. For example, **1f** gave **2f** in 85% yield in the absence of solvents. However, this latter protocol is limited to substrates that are liquid at the reaction temperature. In addition, the catalyst recycling appears less obvious.

Next we investigated the extension of the above protocol to a domino annulation–alkylation process for the preparation of 2,3-disubstituted indoles **3** from 2-alkynylanilines **1** and α,β-enones (Scheme 2a). However, in contrast to the previously reported results in EtOH,[10b] the analogous reaction of **1a** with 3-buten-2-one in [bmim]BF_4 led exclusively to the aza-Michael addition product **4a** in excellent isolated yield (Scheme 2b). Though the desired indole derivative **3a** was not obtained, it is worth emphasizing that gold catalysis in ionic liquids appears to provide a convenient route to aza-Michael addition products[18] and holds promise as an efficient tool to overcome some of the drawbacks of traditional methods.[19]

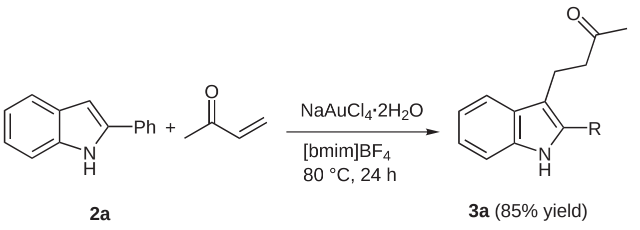
Eventually, we were pleased to find that 2,3-disubstituted indoles **3** could be prepared by the ionic liquid-based protocol in a single, practical one-flask operation by adding 3-buten-2-one to the reaction mixture after completion of the annulation step (HPLC analysis) and increasing the reaction temperature to 80 °C (Scheme 3). Control experiments revealed that **2a** can be converted into **3a** in 85% yield upon treatment with 3-buten-2-one in the presence of 1% of $NaAuCl_4{\cdot}2H_2O$ at 80 °C for 24 hours (Scheme 4).



Scheme 2

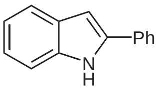
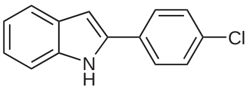
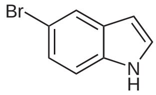
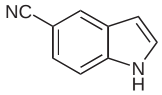


Scheme 3



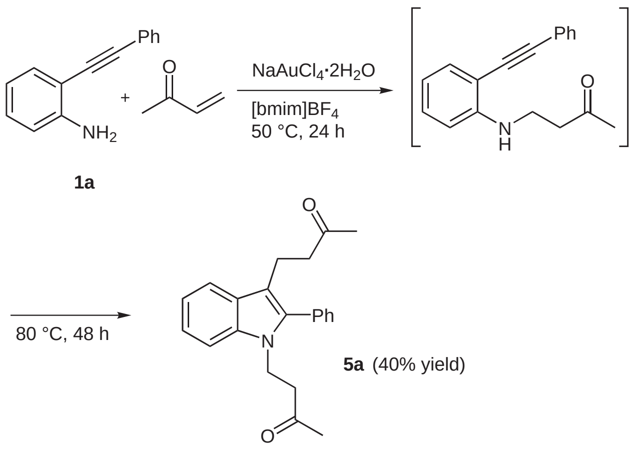
Scheme 4

Table 3 Gold-Catalyzed Alkylation of Indoles with 3-Buten-2-one

Entry	Indole **2**	3-Alkylindole **3** Yield (%)[b]
1	 **2a**	**3a** (85)
2	 **2b**	**3b** (95)
3	 **2g**	**3g** (95)
5	 **2h**	**3h** (90)

[a] Reactions were carried out on a 0.26-mmol scale in [bmim]BF$_4$ (1.0 mL) at 80 °C for 24 h using the following molar ratios: **2**/3-buten-2-one/NaAuCl$_4$·2H$_2$O = 1:3:0.01.

[b] Yields refer to single runs and are for pure isolated products.



Scheme 5

Then, the gold-catalyzed alkylation of indoles[20] with 3-buten-2-one in [bmim]BF$_4$ was extended to other substrates and the results obtained are summarized in Table 3. The reaction gave excellent results even with indolyl rings containing electron-withdrawing groups [e.g. 5-bromoindole (**2g**) and 5-cyanoindole (**2h**)].

As an example, we also applied the one-flask protocol to the preparation of the trisubstituted indole **5a** from **1a** through a process based on the aza-Michael addition–annulation–alkylation sequence (Scheme 5).

We have not investigated the nature of the active catalyst species under our conditions, but it is likely that a species different from the added one is involved. Indeed, hints indicative of the non-innocuous nature of imidazolium-based ionic liquids as well as the formation of carbene species and nanoparticles in the presence of palladium catalysts have been observed.[21] Application of a gold(I)-carbene complex as a catalyst for the hydroamination of unactivated alkenes has been reported.[22] Clearly, further studies are needed to clarify the nature of the active catalyst in the present reactions.

The recyclability of the catalyst system in [bmim]BF$_4$ was then examined for the annulation of **1a** to **2a**. The nature of the gold salt was found to play a pivotal role in the reutilization of the catalyst system. Only n-Bu_4NAuCl_4 was recycled and reused for more than five runs[23] without any significant loss of the catalyst activity (Table 4).

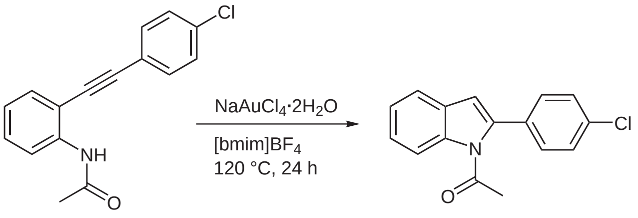
Table 4 Recycling Studies for the Cyclization of **1a** to **2a** in [bmim]BF_4 in the Presence of n-Bu_4NAuCl_4[a]

Run	Yield of **2a** (%)[b]
1	98
2	98
3	97
4	98
5	85

[a] Reactions were carried out on a 0.52-mmol scale in [bmim]BF_4 (2.0 mL) at 50 °C for 24 h using the following molar ratio: **1**/n-$Bu_4NAuCl_4 \cdot 2H_2O$ = 1:0.01.
[b] Determined by HPLC analysis.

To optimize this synthetic approach in terms of reaction time, the cyclization of **1a** to **2a** was also attempted under microwave irradiation conditions, which are known to accelerate the gold-catalyzed homogeneous reactions.[24] Using multimode irradiation with internal temperature control, **2a** was obtained in quantitative yield in 15 minutes at 100 °C. By comparison, one hour of conventional heating was required at the same temperature to obtain **2a** in 90% yield.

Finally, the cyclization of 2-alkynylanilide **6a** was briefly investigated (Scheme 6). Below 120 °C the reaction failed to give the desired product, most probably because of solubility problems. At 120 °C the indole derivative **7a** was formed in 90% yield after 24 hours. This result shows that the amide **6a** is less reactive than the amine **2a** in this cyclization process, very likely because of the lower nucleophilicity of the nitrogen atom.



6a **7a** (90% yield)

Scheme 6

In summary, we have shown that catalysis by gold in [bmim]BF_4 can represent an efficient tool for the cyclization of 2-alkynylanilines to 2-substituted indoles. The nature of the gold salt plays a key role in the recyclability and reuse of the catalyst system. 2-Alkynylanilides are less reactive than 2-alkynylanilines. The reaction times can be significantly reduced using microwave irradiation. One-flask annulation–alkylation and aza-Michael addition–annulation–alkylation procedures can provide an easy entry into 2,3-disubstituted and 1,2,3-trisubstituted indoles, respectively.

Acknowledgment

The authors are greatly indebted to the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, the University 'La Sapienza' and the University of L'Aquila for financial support of this research.

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(16) [bmim]$AuCl_4$ was prepared as follows: To a magnetically stirred solution of [bmim]Cl (0.0458 g, 0.263 mmol) in CH_2Cl_2 (5 mL) was added $NaAuCl_4{\cdot}H_2O$ (0.100 g, 0.263 mmol) and the reaction was allowed to stand at r.t. for 4 h. Then, the mixture was extracted with CH_2Cl_2 (100 mL) and H_2O (2 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated to give [bmim]$AuCl_4$ as a yellow powder (0.120 g).

(17) **Representative Procedure**: To 2-(dec-1-ynyl)aniline (**1f**; 0.059 g, 0.26 mmol) in [bmim]BF_4 (1 mL) was added $NaAuCl_4{\cdot}2H_2O$ (0.001 g, 1 mol%). The mixture was stirred at 50 °C for 24 h. The mixture was diluted with Et_2O (100 mL) and washed with brine. The Et_2O layer was dried (Na_2SO_4) and concentrated in vacuo and the residue was purified by flash chromatography on silica gel giving **2f** (54 mg, 92% yield); mp 50–51 °C. IR (KBr): 3413, 2923, 1457, 1408, 774 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.86$ (br s, 1 H), 7.57 (d, $J = 7.6$ Hz, 1 H), 7.32 (d, $J = 7.7$ Hz, 1 H), 7.25 (dt, $J_1 = 7.7$ Hz, $J_2 = 1.3$ Hz, 1 H), 7.11 (dt, $J_1 = 7.6$ Hz, $J_2 = 1.0$ Hz, 1 H), 6.27 (s, 1 H), 2.78 (t, $J = 7.6$ Hz, 2 H), 1.75 (quin, $J = 7.5$ Hz, 2 H), 1.23–1.48 (m, 10 H), 0.93 (t, $J = 7.6$ Hz, 3 H). ^{13}C NMR ($CDCl_3$): $\delta = 140.1$, 136.9, 128.9, 121.0, 119.8, 119.6, 110.3, 99.5, 31.9, 29.5, 29.4, 29.28, 29.26, 28.3, 22.7, 14.2. Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found: C, 83.71; H, 10.13; N, 6.15. MS: *m*/*z* (%relative intensity) = 229 (50) [M^+], 144 (41), 131 (81), 130 (100).

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(23) **Recycling Procedure**: To a solution of **1a** (0.100 g, 0.52 mmol) in [bmim]BF_4 (2 mL) was added *n*-Bu_4NAuCl_4 (0.003 g, 1 mol%). The mixture was stirred at 50 °C for 24 h. The product was extracted from the reaction mixture by addition of Et_2O (5 × 10 mL). The Et_2O layer was separated. The ionic liquid layer containing the gold catalyst was pumped for several minutes and reused.

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