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Addition of Indoles to Oxyallyl Cations for Facile Access to α-Indole Carbonyl Compounds

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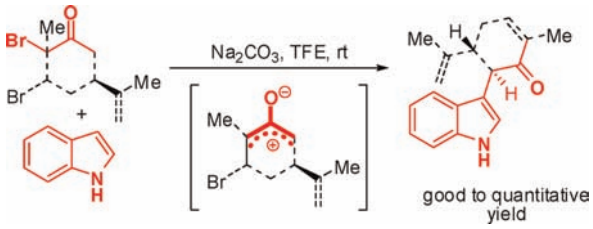
ABSTRACT



A direct coupling of unprotected indoles and α-halo ketones *via in situ* generated oxyallyl cation intermediates is described. The reactions efficiently afford α-indole carbonyl compounds with good to quantitative yields.

α-Indole carbonyl compounds are important building blocks for the concise preparation of synthetic or naturally occurring bioactive molecules, such as *β*-carbolines, carbazoles, serotonins, tryptophols, hapalindole Q, and Fishcherindole U (Figure 1).[1] The synthesis of α-indole carbonyl compounds can be realized *via* multistep protocols,[2] such as epoxide opening by indole magnesium chlorides followed by oxidation,[3] reactions of Weinreb amides with Grignard reagents,[4] base-promoted condensation between protected indoles and ketones followed by hydroxylation and oxidation,[5] and other cross-coupling methods,[6] in which substrate protection and prefunctionalization are typically required. Baran and co-workers recently developed the direct coupling of unprotected indoles with *in situ*

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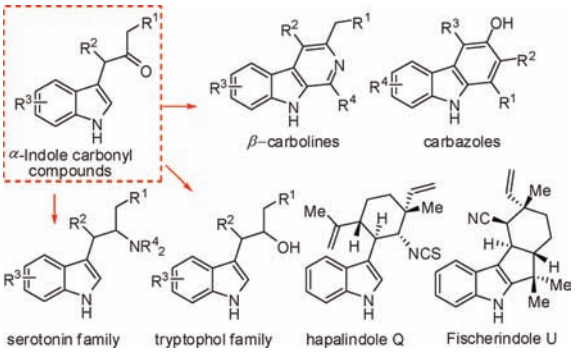
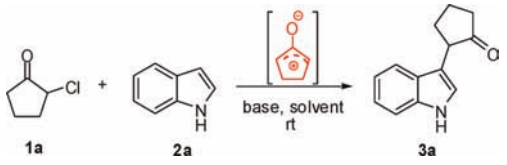


Figure 1. Natural products synthesized from α-indole carbonyls.

generated enolates to prepare α-indole carbonyl compounds.[7] By using a slight excess amount of the indole to avoid homocouplings of the enolates, the Baran group has applied this strategy to rapidly construct a diverse set of indole-containing natural products, such as hapalindoles, Fischerindoles, ketorolac, and acremoauxin A.[8]

Table 1. Model Reaction Optimization[a]



entry	base	solvent	time [h]	yield [%][b]
1	Na_2CO_3	solvents[c]	48	<5
2	Na_2CO_3	H_2O	4	22
3	Na_2CO_3	MeOH	12	50
4	$NaHCO_3$	TFE	48	<5
5	NaOH	TFE	4	60
6	pyrrolidine	TFE	48	79
7	Et_3N	TFE	48	83
8	**Na_2CO_3**	**TFE**	**12**	**>95**
9	Na_2CO_3	HFIP	16	91

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), base (0.6 mmol) in solvent (1 mL) at rt. [b] Isolated yield of **3a**. [c] DMF, DMSO, THF, Et_2O, toluene, CH_2Cl_2, EtOAc, CH_3CN. TFE = 2,2,2-trifluoroethanol; HFIP = hexafluoro-2-propanol.

We are interested in developing alternative methods for efficient access to α-indole carbonyls. Oxyallyl cations derived from α-chloroketones caught our attention in part due to synthetic simplicity and potential to develop enantioselective catalysis. These oxyallyl cations have been extensively explored in the context of (4 + 3) cycloadditions with dienes.[9] The interrupted processes (i.e., simple nucleophilic addition to the oxyallyl cations), however, often give poor yields and thus show limited utilities.[10] Here we report a direct nucleophilic addition of unprotected indoles to *in situ* generated oxyallyl cations for an efficient access to α-indole carbonyl compounds (Table 1). The oxyallyl cations are formed from α-chloroketones under mild conditions, and some of the products can be obtained in pure form after a simple filtration, further highlighting the practical utilities of this method. It is worth noting that oxyallyl cations could also be generated during Nazarov cycloadditions to be trapped by indole nucleophiles, as disclosed by the groups of Burnell[11] and Tius.[12]

We first studied the reaction between 2-chlorocyclopentanone (**1a**) and indole (**2a**). Little product (**3a**) was obtained using common organic solvents such as DMSO, THF, and toluene in the presence of Na_2CO_3 (Table 1, entry 1). The use of water or methanol as solvent led to **3a** with low to moderate yields, in part due to side reactions between these nucleophilic solvents and the oxyallyl cation intermediates (Table 1, entries 2 and 3).[13] Fluorinated alcohols (such as trifluoromethanol, TFE) were then evaluated (Table 1, entries 4–9). With TFE as the solvent, the choice of bases showed a significant effect on the reaction cleanliness and yields. The starting materials (**1a** and **2a**) remained largely unconsumed when relatively weak bases such as $NaHCO_3$ were used. On the other hand, when strong bases such as NaOH were used, the reaction became a little complex with the formation of Favorskii rearrangement[14] adducts, among other side

(10) (a) The Harmata group recently reported a successful ene-type 1 reaction between an oxyallyl cation bearing a good leaving group (Me_2PhSi group) and enol ethers. Without the Me_2PhSi group, an inseparable mixture of both ene-type **1** product and (4 + 3) cycloadduct was produced. See: Harmata, M.; Huang, C.; Rooshenas, P.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 8696. (b) Harsh conditions (e.g., high temperature, strong acid) have also been used to generate oxyallyl cations from other functionalized ketones for nucleophilic reactions with low to moderate yields; see: Leitich, J.; Heise, I. *Eur. J. Org. Chem.* **2001**, 2707. (c) Freter, K. *Liebigs Ann.* **1978**, 1357.

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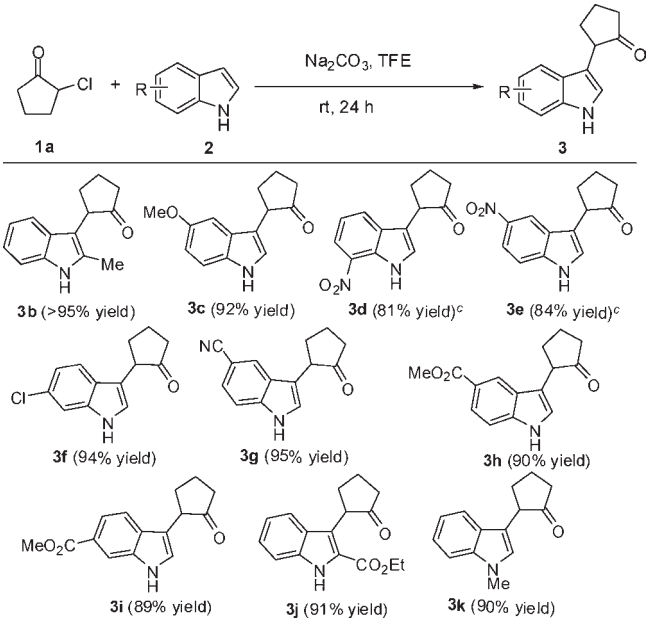
(16) Another possible pathway involving the addition of indole to the ketone carbonyl group followed by a cyclopropane formation and cleavage is ruled out, as this will lead to a different regioisomer of **4b** from **1d**, contrary to our observation. For relevant studies, see: (a) Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7440. (b) Yasuda, M.; Tsuji, S.; Shibata, I.; Baba, A. *J. Org. Chem.* **1997**, *62*, 8282. (c) Kelin, A. V.; Kulinkovich, O. G. *Synthesis* **1996**, 330. (d) Yasuda, M.; Katoh, Y.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 4386. (e) Yasuda, M.; Oh-Hata, T.; Shibata, I.; Baba, A.; Matsuda, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 859. (f) Baba, A.; Yasuda, M.; Yano, K.; Shibata, I.; Matsuda, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207. (g) Kosugi, M.; Takano, I.; Sakurai, M.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, *13*, 1221.

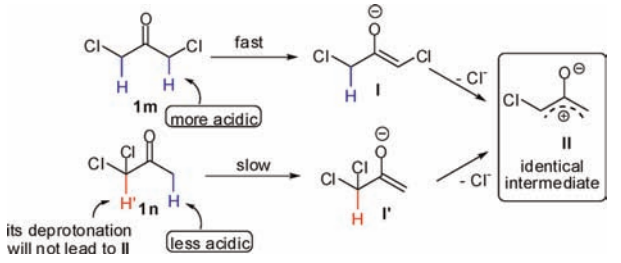
products (Table 1, entry 5). Finally we found that organic bases such as pyrrolidine and Et_3N, and inorganic bases such as Na_2CO_3 could effectively promote the reaction (Table 1, entries 6–9). Using Na_2CO_3 in TFE, a very clean reaction was realized with quantitative formation of **3a**, obtained in essentially pure form after a simple filtration and solvent evaporization (Table 1, entry 8). The high ionizing power and low nucleophilicity of the fluorinated solvents are believed to contribute to the cleanliness and high yield of the reactions.[15]

Scheme 1. Addition of Different Indoles to **1a**[a,b]



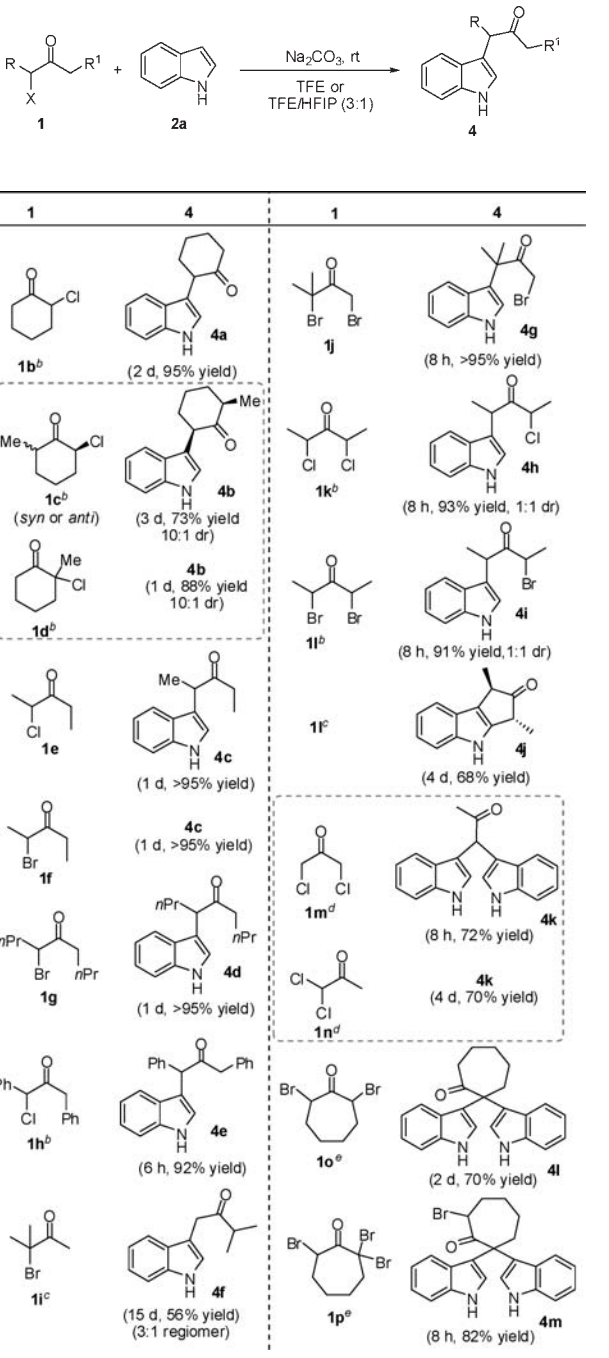
[a] **1a** (0.5 mmol), **2** (0.5 mol), Na_2CO_3 (0.6 mmol) in TFE (1 mL). [b]Isolated yield. [c] **1a** (0.60 mmol) and Na_2CO_3 (0.75 mmol) were used.

Scheme 2. Mechanistic Studies



Next, we examined different indoles in the reaction with **1a**. Both electron-rich and -deficient indoles reacted well to give **3** in good to excellent yields (Scheme 1, **3b**–**3j**). One notable variation was that indoles substituted with very strong electron-withdrawing functionalities ($-NO_2$) required a slight excess of **1a** (1.2 equiv) and base (1.5 equiv) to drive the reaction to its completion (**3d** and **3e**). The reaction outcome remained unaffected with different substitution patterns on the indoles (**3h**–**3j**). We also

Table 2. Addition of Indole to Different α-Halo Ketones[a]



[a] **1** (0.5 mmol), **2a** (0.5 mmol), Na_2CO_3 (0.6 mmol) in TFE (1 mL); no column chromatography required. [b] **1** (0.6 mmol), Na_2CO_3 (0.7 mmol). [c] TFE/HFIP (0.9 mL + 0.3 mL) as solvent. [d] **1** (2.5 mmol), TFE/HFIP (0.9 mL + 0.3 mL) as solvent. [e] **2a** (2.5 mmol).

examined *N*-protected indoles: *N*-methyl indole gave the product in excellent yield (Scheme 1, **3k**), and *N*-phenylsulfonyl indole remained unreacted.

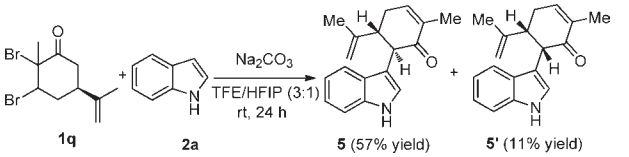
We then evaluated the addition of indole to different α-haloketones (**1**), as summarized in Table 2. The same product (**4b**) was obtained starting with two different isomers of chloro-2-methyl-cyclohexanone (**1c** and **1d**), suggesting an S_N1 reaction pathway *via* the same oxyallyl

cation intermediate (Scheme 2).[16] Similarly, the two isomers of dichloroacetone (**1m** and **1n**) gave the identical product (**4k**). A significant difference in the reaction time was observed for 1,3-dichloroacetone **1m** (8 h) and 1,1-dichloroacetone **1n** (4 days). This difference can be explained by the relative ease of oxyallyl cation formations from the two chloro ketone isomers (**1m** and **1n**), as illustrated in Scheme 2. 1,3-Dichloroacetone **1m** contains a more acidic proton (α-C**H**-Cl; compared to α-C**H**-H of 1,1-dichloroacetone **1n**) which can undergo faster deprotonation to eventually give oxyallyl cation intermediate **II**. These results also suggest that the oxyallyl cation formation is likely the rate-determine step for the indole addition reactions. The same hypothesis explains the longer reaction time and requirement for a higher ionizing solvent (HFIP, instead of TFE) for **1i**, compared to **1j** (Table 2).

As for the scope of the reaction regarding the haloketone substrates, dichloro or dibromo ketones (**1j**–**l**) in reaction with an equimolar amount or excess of indole gave the monosubstitution products in excellent yields (Table 2, **4g**–**4i**). With an extended reaction time in TFE/HFIP, **1l** (and **1k**) could undergo a second (intramolecular) nucleophilic addition *via* **4i** to give an indole-fused multicyclic ketone product **4j** in 68% yield and essentially as a single diastereomer. It is interesting to note that such intramolecular reactions were not observed while using other dihaloketones **1j** and **1m**–**p**. In the cases using **1m**–**p**, two molecules of indole reacted with one molecule of ketone to give **4k**–**m**. No product was observed with **1i**, **1m**, and **1n** using TFE as the solvent, even at reflux temperature. We also tested α-haloketones such as 2-bromo-1-phenyl ethanone and 1-bromo-3,3-dimethyl butan-2-one under the above reaction conditions. As expected these substrates remained unreacted as they could not form oxyallyl cations.

The utility of our method is further illustrated with the synthesis of a key intermediate in the total synthesis of hapalindole Q. Dibromoketone **1q** and indole **2a** were subjected to a base-promoted coupling reaction in TFE/HFIP to give **5** with 57% isolated yield (the minor diastereomer was isolated in 11% yield, Scheme 3). Adduct **5** is the key intermediate in Baran's total syntheses of several natural products including hapalindole Q.[7,8b,8c]

Scheme 3. Synthesis of the Key Intermediate **5** of Hapalindole



In conclusion, we have developed a highly efficient and practical method for the direct coupling of indoles and α-halo ketones. The α-indole carbonyl compounds were obtained in good to quantitative yields, and in many cases analytically pure products were obtained after simple filtrations followed by solvent removal. No protection or prefunctionalization of the indole substrates is required in our protocol. Compared to the cycloaddition reactions, direct nucleophilic additions to oxyallyl cations (and their analogs or equivalents) have remained underdeveloped. Further development of these S_N1-type direct coupling reactions, including their asymmetric catalytic versions, is being pursued in our laboratory.

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Supporting Information Available. Experimental procedures, compound characterization, NMR spectra, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.