ChemInform Abstract: Cu(OTf) 2 -Catalyzed Synthesis of 2,3-Disubstituted Indoles and 2,4,5-Trisubstituted Pyrroles from α-Diazoketones.

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$Cu(OTf)_2$-Catalyzed Synthesis of 2,3-Disubstituted Indoles and 2,4,5-Trisubstituted Pyrroles from α-Diazoketones

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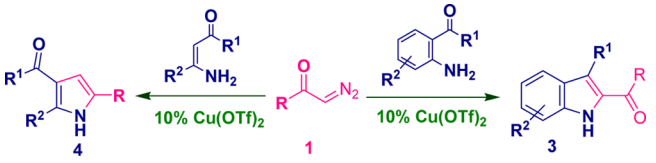
ABSTRACT



A novel method has been devised for the synthesis of 2,4,5-trisubstituted pyrrole derivatives through the coupling of α-diazoketones with *β*-enaminoketones and esters using 10 mol % of $Cu(OTf)_2$. A wide range of 2,3-disubstituted indole derivatives were also prepared from α-diazoketones and 2-aminoaryl or alkyl ketones. The synthetic versatility of this approach has been exemplified in the formal synthesis of homofascaplysin C.

The indole nucleus is often found in various natural products and is known to exhibit a broad spectrum of biological activities (Figure 1).[1] They are being recognized as privileged structures in medicinal chemistry because of their affinity to bind with various receptors. Consequently, several approaches have been developed for the synthesis of indole derivatives, which include the Fisher indole synthesis,[2] the hydroamination of 2-alkynylanilines,[3] metal-catalyzed cascade reactions,[4] an intramolecular C−H amination of azidoacrylates,[5] and the coupling of *N*-aryl amides with ethyl diazoacetate.[6] Recently, the synthesis of 2,3-disubstituted indoles by the nucleophilic addition of phenyldiazoacetate to the *ortho*-imino group[7] has been reported, which are well-known for indole synthesis. In particular, 3-substituted indole derivatives have been prepared through the condensation of 2-aminobenzaldehyde with ethyl diazoacetate *via* a 1,2-aryl shift.[8] Although numerous methods have been reported for the preparation of indoles, simple and expedient approaches still remain scarce. Therefore, the development of efficient methods for the synthesis of indoles from simple precursors continues to be a challenging task. In particular, an annulated pyrrole skeleton is an important structural motif for the

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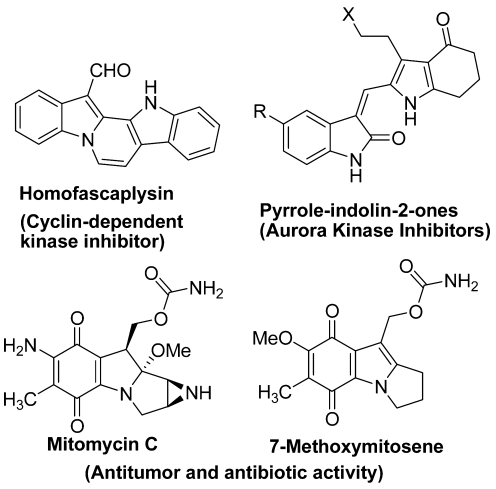
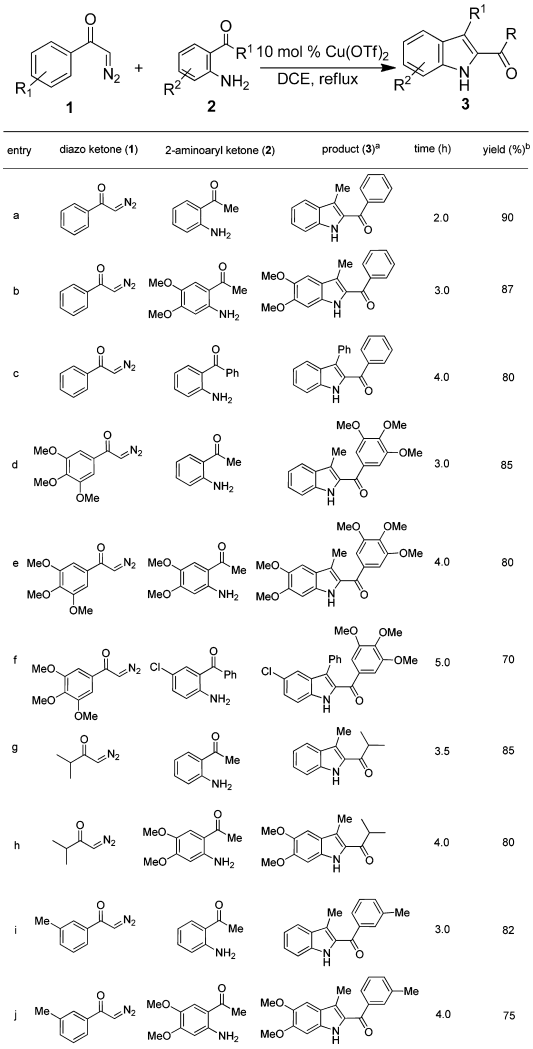


Figure 1. Biologically active indole based molecules.

construction of several indole based heterocycles.[9] Furthermore, a 4-oxo-4,5,6,7-tetrahydroindole core is often present in many biologically important alkaloids such as mitomycins and 7-methoxymitosene.[10] Consequently, a three-component process has been developed for the synthesis of annulated pyrroles through the condensation of α-haloketones with 1,3-cyclohexadiones and ammonia or primary amines.[11] More recently, an elegant approach has been devised for the synthesis of annulated pyrroles from the Morita–Baylis–Hillman acetates which in turn are derived from the 2-oxo-2-(phenyl)acetaldehyde and cyclohexenone.[12] We also explored the synthetic potential of α-diazoketones for the synthesis of biologically active heterocycles such as imidazo[1,2-*a*]pyridines, 2-aminothiozoles, quinoxalines, spirooxindoles, and cyclopropyl glycals.[13] Here, we wish to report an efficient method for the synthesis of 2,3-disubstituted indoles through the coupling of α-diazoketones with 2-aminoaryl ketones while the coupling of α-diazoketones with *β*-enaminoketones or esters affords the corresponding 2,4,5-trisubstituted pyrroles in good yields.

Initially, we attempted the coupling of aryl diazoketone with 2-aminoaryl ketone in the presence of 10 mol % of $Cu(OTf)_2$. Although the reaction proceeds smoothly at 25 °C, it required a prolonged reaction time (12 h) to achieve high conversion. But the rate of reaction was enhanced remarkably by increasing the temperature from 25 to 80 °C. For instance, treatment of phenyldiazoketone (**1a**) with 2-aminoacetophenone (**2a**) in the presence of 10 mol % $Cu(OTf)_2$ in DCE at 80 °C over 2 h afforded the corresponding 3-methyl-2-benzoylindole **3a** in 90% yield. Inspired by the above result, we turned our attention toward investigating the scope of this methodology. To our delight, various aryl diazoketones reacted well with 2-aminoaryl

Table 1. Synthesis of Indoles from α-Diazoketones with 2-Aminoalkyl or arylketones



[a] All tie products were characterized by NMR, IR and mass spectroscopy. [b] Yield refers to pure product after chromatography.

(9) (a) Matsumoto, M.; Ishida, Y.; Watanabe, N. *Heterocycles* **1985**, *23*, 165. (b) Matsumoto, M.; Ishida, Y.; Hatanaka, N. *Heterocycles* **1986**, *24*, 1667. (c) Hatanaka, N.; Ozaki, O.; Matsumoto, M. *Tetrahedron Lett.* **1986**, *27*, 3169. (d) Matsumoto, M.; Watanabe, N. *Heterocycles* **1986**, *24*, 3149. (e) Ishibashi, H.; Tabata, T.; Hanaoka, K.; Iriyama, H.; Akamasu, S.; Ikeda, M. *Tetrahedron Lett.* **1993**, *34*, 489. (f) Ishibashi, H.; Akamatsu, S.; Iriyama, H.; Hanaoka, K.; Tabata, T.; Ikeda, M. *Chem. Pharm. Bull.* **1994**, *42*, 271. (g) Doi, K.; Mori, M. *Heterocycles* **1996**, *42*, 113. (h) Edstrom, E.; Yu, T. *Tetrahedron* **1997**, *53*, 4549. (i) Martinez, R.; Oloarte, J.; Avila, G. *J. Heterocycl. Chem.* **1998**, *35*, 585. (j) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Naruto, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4383. (k) Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060. (l) Arai, M.; Ishikawa, T.; Saito, S.; Miyauchi, Y.; Miyahara, T. *Synlett* **2009**, 122.

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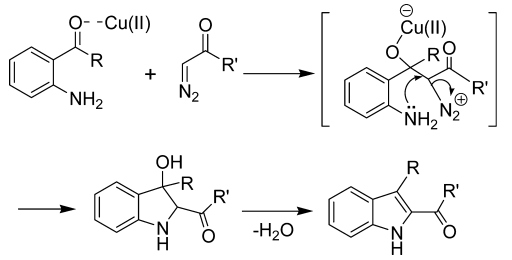
ketones to afford the respective 2,3-disubstituted indoles. Both aryl and alkyl diazoketones participated well in this reaction. Similarly, various 2-aminoacetophenones and 2-aminobenzophenones afforded the desired indole derivatives in good yields (Table 1). A tentative reaction mechanism is proposed in Scheme 1. During the indole formation, the Lewis acid activates the carbonyl group of the aryl ketone to facilitate the nucleophilic attack of the diazo compound. This is followed by displacement of N_2 by aryl amine with subsequent dehydration resulting in the formation of 2,3-disubstituted indoles (Scheme 1).[14] Next

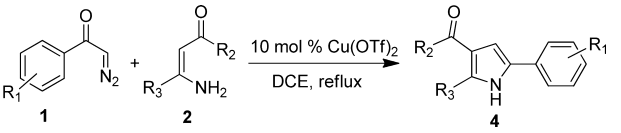
Scheme 1. A Plausible Pathway for the Formation of Indoles



we extended this approach for the synthesis of trisubstituted pyrrole derivatives *via* the coupling of diazoketones with β-enamino ketones or esters. Accordingly, treatment of α-diazoketone with β-enamino ketone in the presence of 10 mol % $Cu(OTf)_2$ in DCE at 80 °C gave the 2,4,5-trisubstituted pyrrole. Several α-diazoketones underwent smooth coupling with β-enamino ketones to provide the corresponding trisubstituted pyrrole derivatives (Table 2). This method also works well with β-enamino esters to furnish the respective pyrrole carboxylates (Table 2, entries b, d, and j). Next we applied this process to the synthesis of annulated pyrroles which are key precursors for many indole based natural products. Thus the coupling of α-diazoketones with β-enaminoketones derived from cyclic 1,3-diketones such as 1,3-cyclohexadione and dimedone gave the corresponding annulated pyrrole scaffolds (entries k and l, Table 2). In contrast, cyclic β-enaminoketones gave the annulated pyrroles in lower yields than acyclic counterparts (Table 2). In the case of enaminoketone, the keto group is less reactive due to its vinylogous amide nature. Therefore, the Lewis acid activates the carbonyl group of the diazo compound which acts as an electrophile and reacts with the amino group of the enamine leading to the pyrrole (Scheme 2). In order to know the effect of solvent and the catalyst, we reacted phenyl diazoketone (**1a**) with 2-aminoacetophenone (**2a**) and 2-enaminoketone (**2**) using various acid catalysts (Table 3) in different solvents. As shown in Table 3, the products **3a** and **4a** were obtained in low yields in THF. Toluene was also found to be ineffective for this reaction. Also, various catalysts such as $Rh_2(OAc)_4$, $Cu(OTf)_2$, CuOTf, $Sc(OTf)_3$, $In(OTf)_3$, $InCl_3$, $BF_3{\cdot}OEt_2$, $InBr_3$,

(14) The authors wish to acknowledge the referee for his valuable input on the reaction mechanism.

Table 2. Synthesis of Pyrroles from α-Diazoketones with 2-Enaminoketones



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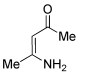
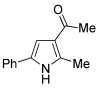
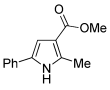
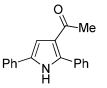
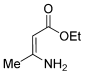
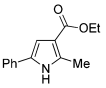
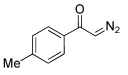
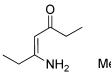
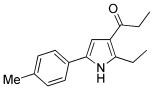
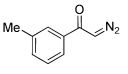
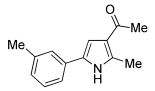
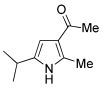
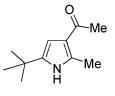
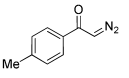
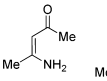
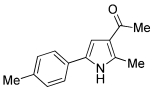
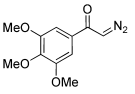
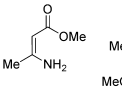
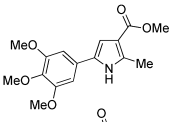
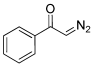
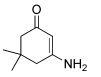
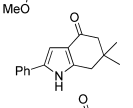
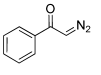
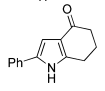
a				6.0	80
b				6.0	78
c				7.0	72
d				6.0	75
e				6.0	80
f				7.0	77
g				6.0	75
h				6.0	70
i				7.0	75
j				6.0	72
k				8.0	55
l				8.0	57

[a] All the products were characterized by NMR, IR, and mass spectroscopy. [b] Yield refers to pure products after chromatography.

$Cu(hfacac)_2$, and $Cu(acac)_2$ were used. Among them, $Cu(OTf)_2$ gave the best results in terms of reaction time and conversion (entry a, Table 3). The solid acid catalysts such as clays, heteropolyacids, and ion-exchange resin were also found to be ineffective in facilitating this reaction.

In both cases, no regioisomers were formed under the reaction conditions as evidenced by the NMR spectra of the crude products. The assigned structures of **3h** and **4d** were further confirmed by X-ray crystallography.

Scheme 2. A Plausible Pathway for the Formation of Pyrroles

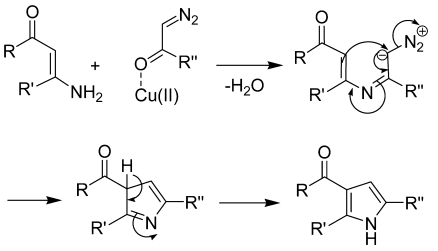


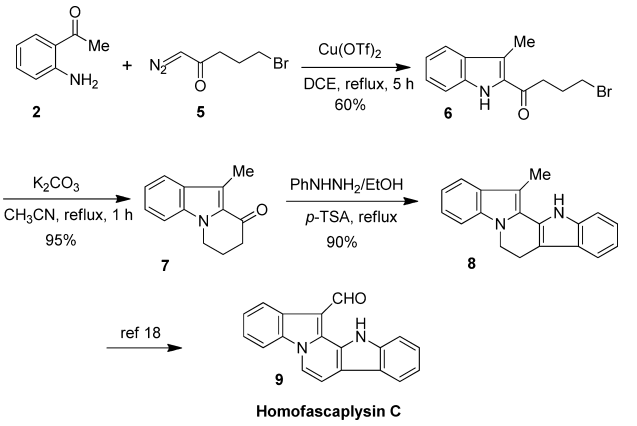
Table 3. Effect of Catalyst and Solvent in the Formation of **3a** and **4a**

entry	acid catalyst	mol %	solvent[a]	time (h)	yield (%)[b] indole (**3a**)	yield (%)[b] pyrrole (**4a**)
a	$Cu(OTf)_2$	10	$ClCH_2CH_2Cl$	6	90	80
b	$Cu(OTf)_2$	10	THF	6	50	30
c	$Cu(OTf)_2$	10	Toulene	6	70	40
d	$Rh_2(OAc)_4$	10	$ClCH_2CH_2Cl$	6	70	80
e	$Cu(hfacac)_2$	10	,,	6	50	50
f	$Cu(acac)_2$	10	,,	6	50	40
g	CuOTf	10	,,	6	80	60
h	$Sc(OTf)_3$	10	,,	6	40	0
i	$InCl_3$	10	,,	6	80	0
j	$In(OTf)_3$	10	,,	6	50	0
k	$InBr_3$	10	,,	6	40	0
l	$BF_3{\cdot}OEt_2$	10	,,	6	10	0
m	PMA	10	,,	6	10	0
n	KSF clay	10	,,	6	0	0
o	Amberlyst-15	10	,,	6	0	0

[a] The reaction was performed at 0.5 mmol scale at reflux. [b] Isolated yield.

Finally, we attempted the synthesis of homofascaplysin C through the coupling of alkyl diazoketone with 2-aminoacetophenone. The pentacyclic pyrido[1,2-*a*:3,4-*b*]-diindole core is found in various natural products such as fascaplysin and homofascaplysin C which were isolated from *Fascaplysinopsis* Bergquist sp. and Fijian sponge *F. reticulata*,[15] respectively. These compounds are found to exhibit a wide range of biological activities.[16] In particular, fascaplysin selectively inhibits the cyclin-dependent kinase, which regulates the G0−G1/S checkpoint of the cell cycle.[17] It also shows antimicrobial activity and cytotoxicity against L-1210 mouse leukemia. Owing to its fascinating biological profiles, fascaplysin can be used as a lead compound for creating novel anticancer drugs. As a result, several methods have been devised for the synthesis of fascaplysin.[18] To show the synthetic utility, we applied the present protocol to the formal synthesis of homofascaplysin C. Accordingly, the coupling of 2-aminoacetophenone (**2**) with diazoketone (**5**) in the presence of 10% $Cu(OTf)_2$ gave the 2,3-disubstitued indole (**6**) in 60% yield. Subsequent base catalyzed intramolecular cyclization of **6** afforded the compound **7** in 95% yield. Further treatment of **7** with phenylhydrazine in the presence of *p*-TSA in ethanol at 80 °C gave the pyridodiindole **8** in 90% yield with high regioselectivity, as the keto group does not have methylene protons at both α-positions. The oxidation of **8** under known conditions affords the target molecule (Scheme 3).[19]

Scheme 3. A New Approach to the Synthesis of Homofascaplysin C



In conclusion, we have demonstrated a novel protocol for the synthesis of 2,3-disubstituted indoles and 2,4,5-trisubstituted pyrrole derivatives in good yields via the coupling of α-diazoketones with 2-aminoketones and *β*-enaminoketones respectively. This is the first example of the synthesis of pyrrole derivatives through the coupling of diazoketones with enaminoketones. This method is also illustrated by the formal synthesis of homofascaplysin C. This approach is very useful for the synthesis of indole-based natural products, especially, 7-methoxymitosene.[20]

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Supporting Information Available. Experimental details, characterization data of products, ^1H and ^{13}C NMR spectra of products, and X-ray crystallography data for **3h** and **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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