Tandem Reactions

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Concise One-Pot Tandem Synthesis of Indoles and Isoquinolines from Amides**

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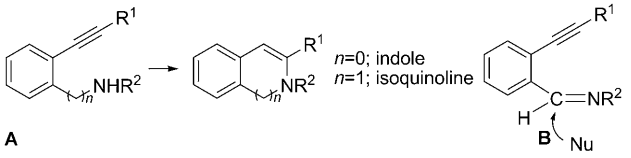
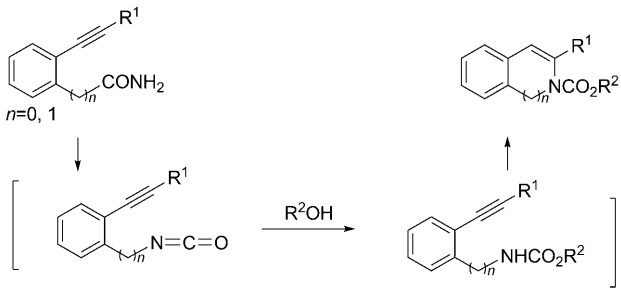
The synthesis of heterocyclic compounds has attracted a great deal of attention because of their biological activities. In particular, the synthesis of indole and isoquinoline frameworks by intramolecular ring closure reactions of 2-alkynylbenzene derivatives **A** is one of the most efficient approaches for the construction of benzo-fused nitrogen heteroaromatic systems.[1,2] We have previously reported the synthesis of 1,2-dihydroisoquinolines using an $In(OTf)_3$-catalyzed tandem nucleophilic addition and cyclization of 2-alkynylarylaldimines **B** (Scheme 1).[3] As part of our continued interest in the



Scheme 1. Tandem approach to indoles and isoquinolines from the ring closure of **A** or **B**.

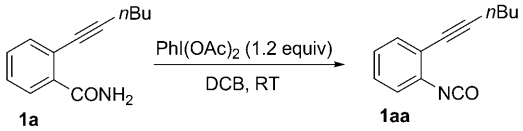
synthesis of biologically active heteroaromatic compounds, we focused on 2-alkynylphenyl, and 2-alkynylphenylmethyl isocyanates. Nucleophilic addition of an alcohol to the isocyanate, followed by intramolecular addition of the resulting carbamate to an activated alkyne, would occur in a tandem manner as a single synthetic operation to give indole and isoquinoline derivatives, respectively. We reasoned that the isocyanate derivatives would be a superior substrate for the construction of the heterocycles compared with 2-alkynylarylaldimines in terms of 1) the more electrophilic nature of the isocyanate carbon; 2) the higher reactivity of the resulting carbamate nitrogen atom toward an alkyne functionality;[4] and 3) easier access from the corresponding stable amides using a Hofmann-type rearrangement[5,6] (Scheme 2). The success of this strategy would depend on whether the



Scheme 2. Synthetic approach to indoles and isoquinolines from amides.

reactivity of the metal that is required for cyclization could be retained in the presence of co-products generated in the Hofmann-type rearrangement. Herein, we report the first concise one-pot tandem synthesis of indoles and isoquinolines from amides.

The Hofmann-type rearrangement reaction between 2-(1-hexynyl)benzamide (**1a**) and $PhI(OAc)_2$[5] in 1,2-dichlorobenzene (DCB) at room temperature proceeded smoothly to afford 2-(1-hexynyl)phenyl isocyanate **1aa** in high yield[7] (Scheme 3). After completion of the Hofmann-type rearrangement was confirmed by thin-layer chromatography, we then considered the viability of subsequent indole formation from the crude mixture by adding $PtCl_2$, ethanol, and NEt_3. Triethylamine was used to neutralize acetic acid formed during the reaction. The desired indole **2a** was obtained in only 9% yield, together with 64% of carbamate **3**, after 3 h at 100°C (Table 1, entry 1). Contrary to our expectations, the reaction without Et_3N went to completion in 0.5 h to give **2a** in 82% yield (Table 1, entry 2). This result implies that $PtCl_2$-catalyzed cyclization proceeds preferentially under acidic condition. To simplify the method, a simultaneous procedure was examined. When a solution of **1a** in DCB, in the presence of $PhI(OAc)_2$, $PtCl_2$, and ethanol, was heated at 100°C, **2a** was produced in 85% yield without a decrease in the reactivity of $PtCl_2$ (Table 1, entry 3). The same reaction at 70°C required a longer reaction time (Table 1, entry 4). Other



Scheme 3. Hofman-type rearrangement of 2-(1-hexynyl)benzamide **1a**.

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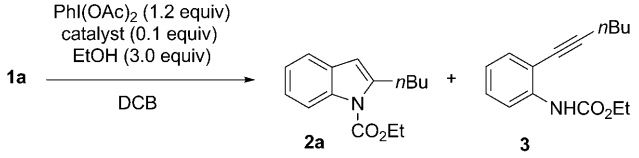
Table 1: Optimization of catalyst and reaction conditions.



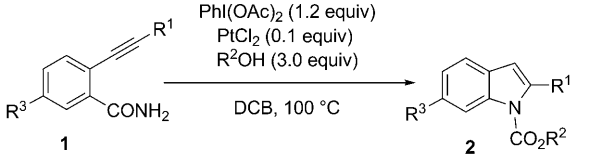
Entry	Catalyst	Conditions	Yield [%]	
			2a	**3**
1[a]	1) $PhI(OAc)_2$ 2) $PtCl_2$, EtOH, Et_3N (3 equiv)	100 °C, 3.0 h	9	64
2[a]	1) $PhI(OAc)_2$ 2) $PtCl_2$ EtOH	100 °C, 0.5 h	82	0
3	$PhI(OAc)_2$, $PtCl_2$, EtOH	100 °C, 0.5 h	85	0
4	$PhI(OAc)_2$, $PtCl_2$, EtOH	70 °C, 2.5 h	84	0
5	$PhI(OAc)_2$, $PdCl_2$, EtOH	100 °C, 2.5 h	78	0
6	$PhI(OAc)_2$, $Pd(OAc)_2$, EtOH	100 °C, 3.0 h	6	62
7	$PhI(OAc)_2$, $CuCl_2$, EtOH	100 °C, 3.0 h	0	84
8	$PhI(OAc)_2$, $Cu(OTf)_2$, EtOH	100 °C, 3.0 h	4	93
9	$PhI(OAc)_2$, $InBr_3$, EtOH	100 °C, 3.0 h	0	92

[a] Stepwise procedure.

metal catalysts, some of which were used in previous studies for intramolecular cyclization of 2-alkynylaniline derivatives,[1–3] did not give satisfactory results (Table 1, entries 5–9).

Having established optimal reaction conditions, we examined the scope of the reaction for various 2-alkynylbenzamides **1a**–**1i** (Table 2). The substitution pattern on the aromatic ring did not affect the reaction efficiency; in the presence of electron-withdrawing groups or electron-donating groups, the yield of indole product was within the range 82–91% (Table 2, entries 1–3). Alkylnylbenzamide **1e**, bearing a phenyl group on the acetylene terminus, gave the corresponding indole (**2e**) in good yield (84%; Table 2, entry 4), although the similar *p*-tolyl-substituted substrate **1f** afforded a noticeably lower yield (66%; Table 2, entry 5). A tosyloxy functional group was tolerated under the reaction conditions to afford the corresponding indole in excellent yield (Table 2, entry 6). Unfortunately, the terminal alkyne **1h** was not suitable for this reaction, resulting in a 33% yield of **2h** (Table 2, entry 7). This result may be due to the known dimerization of terminal acetylenes with $PhI(OAc)_2$.[8] The reaction of trimethylsilyl-protected substrate **1i** revealed desilylation to furnish **2h** in moderate yield (66%, Table 2, entry 8). Using benzyl alcohol as a nucleophile, the *N*-Cbz-protected indole (Cbz = phenylmethoxycarbonyl) was obtained in good yield (Table 2, entry 9) although the use of *tert*-butanol resulted in only a 34% yield of **2k**, which is probably due to steric hindrance from the bulky nucleophile (Table 2, entry 10).

Table 2: Tandem indole formation from 2-alkynylbenzamide.

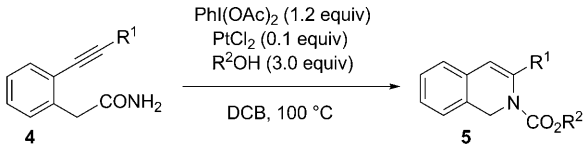


Entry	**1**	R^1	R^2	R^3	*t* [h]	**2**	Yield [%]
1	**1b**	*n*Bu	Et	F	2	**2b**	84
2	**1c**	*n*Bu	Et	NO_2	2	**2c**	91
3	**1d**	*n*Bu	Et	OMe	2	**2d**	82
4	**1e**	Ph	Et	H	2.5	**2e**	84
5	**1f**	*p*-Tol	Et	H	1	**2f**	66
6	**1g**	$(CH_2)_3OTs$	Et	H	2	**2g**	100
7	**1h**	H	Et	H	24	**2h**	33
8	**1i**	TMS	Et	H	3	**2i**	0[a]
9	**1a**	*n*Bu	Bn	H	1	**2j**	90
10	**1a**	*n*Bu	*t*Bu	H	3	**2k**	34

[a] Desilylated indole **2h** was obtained in 66% yield.

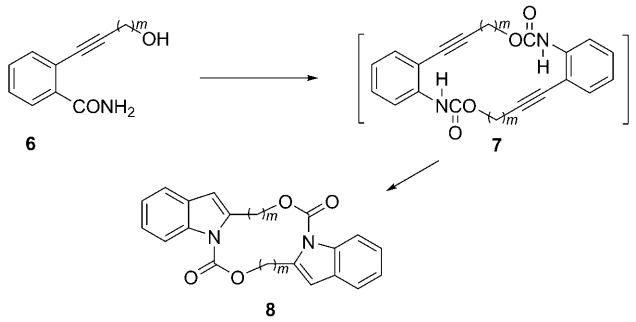
To further examine the scope and limitation of our tandem Hofmann-type rearrangement and cyclization strategy, this procedure was applied to the construction of dihydroisoquinolines **5** from 2-alkynylbenzylamides **4**, which are one-carbon homologues of 2-alkynylbenzamides **1**. The reactions of **4a** and **4b** with different alcohols proceeded smoothly under the optimized reaction conditions to give isoquinolines **5a**–**5d** in good yields (Table 3, entries 1–4). The alkynylbenzylamide **4c**, which has an aliphatic substituent on the acetylene terminal position, also afforded the corresponding isoquinoline **5e** in moderate yield (66%; Table 3, entry 5). The structure of compound **5c** was confirmed by X-ray crystallography.[9] Cyclization occurred via a 6-*endo* mode to produce **5** as the sole product; 5-*exo*-cyclized products were not obtained at all. The indoles and isoquinolines synthesized herein contain enecarbamate frameworks, which are attractive synthetic intermediates owing to their applicability to synthetic transformations.[10]

Table 3: Tandem dihydroisoquinoline formation from 2-alkynylbenzylamide.



Entry	**4**	R^1	R^2	*t* [h]	**5**	Yield [%]
1	**4a**	Ph	Et	1	**5a**	86
2	**4a**	Ph	Me	1	**5b**	92
3	**4a**	Ph	Bn	1	**5c**	92
4	**4b**	*p*-Tol	Et	1	**5d**	82
5	**4c**	*n*Bu	Et	3	**5e**	66

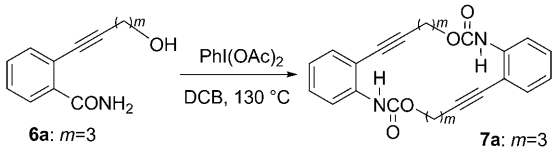
We then investigated the extension of this procedure to the dimerization reaction,[11] using 2-alkynylbenzamides **6** bearing a ω-(hydroxy)alkyl group as substrates. We expected cyclodimerization involving consecutive intermolecular and intramolecular carbamate formation, with subsequent platinum(II)-catalyzed transannular[12] hydroamination to macrocyclic bis(indole) **8** from bis(yne carbamate) **7** (Scheme 4). First, we examined the reaction of compound **6a** with $PhI(OAc)_2$. We anticipated that the concentration of the reaction solution may play an important role in the reaction efficiency. Thus, several different concentrations (0.005–0.5 M)



Scheme 4. Synthetic approach to macrocyclic bis(indole)s.

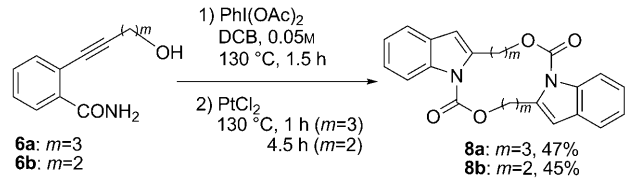
were examined at 130 °C and twenty-membered ringed bis(yne carbamate) **7a** was obtained in 35–62% yield (Table 4). The optimal concentration for the production of **7a** was found to be between 0.01 M and 0.05 M (Table 4, entries 2 and 3); the structure of **7a** was confirmed by X-ray crystallography.[9] These macrocyclic compounds have been the subject of recent interest owing to their potential biological activities.[13]

Table 4: Macrocyclic bis(yne carbamate) synthesis.



Entry	conc. [mol L^{-1}]	*t* [h]	**7a** yield [%]
1	0.005	5	39
2	0.01	5	62
3	0.05	2	62
4	0.1	1	48
5	0.5	1	35

Finally, we applied the stepwise procedure to the macrocyclic bis(indole) synthesis. Treatment of a 0.05 M solution of amides **6** with $PhI(OAc)_2$ at 130 °C for 2 h, followed by cyclization with $PtCl_2$ at 130 °C for 1–4.5 h, afforded the desired indoles **8** via macrocyclic bis(yne carbamate) intermediates **7**. The yields of **8a** and **8b** were moderate,[14] because of the formation of a complex mixture (Scheme 5).[15] The structure of compound **8a** was also confirmed by X-ray crystallography.[9]



Scheme 5. Macrocyclic bis(indole) synthesis.

In summary, we have developed a concise one-pot platinum(II)-catalyzed synthesis of indoles and isoquinolines from isocyanates which are derived from a Hofmann-type rearrangement of amides using a hypervalent iodine reagent. Furthermore, interesting C_2-symmetrical macrocyclic bis(yne carbamate) have been efficiently synthesized by cyclodimerization of 2-(ω-hydroxy-1-alkynyl)benzamides. This discovery led to the use of transannular cyclization to furnish macrocyclic bis(indole) in moderate yields. Further studies involving macrocyclic frameworks are in progress.

Experimental Section

General procedure for the tandem indole synthesis: Alcohol (0.15 mmol) was added to a solution of 2-alkynylbenzamide (0.05 mmol), $PhI(OAc)_2$ (0.06 mmol), and $PtCl_2$ (0.005 mmol), in 1,2-dichlorobenzene (0.5 mL), and the mixture was stirred at 100 °C. The crude reaction mixture was purified using silica gel chromatography to afford the indole product.

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[14] The yields of bis(indole)s **8** were better with the stepwise procedure than with the simultaneous procedure.
[15] For example, trimeric indole was obtained as a minor product from **6a**. Details of the complex mixture are currently under investigation.

