Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Meixiang Liao, Xiaoyun Zhang & Pengfei Yue (2018) TEMPO/CuI synergetic catalyzed oxidative cross-coupling of indoles with benzylamines: Synthesis of bis(indolyl)phenylmethanes, Synthetic Communications, 48:13, 1694-1700, DOI: 10.1080/00397911.2018.1459722

To link to this article: https://doi.org/10.1080/00397911.2018.1459722

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 13, 1694–1700
https://doi.org/10.1080/00397911.2018.1459722

TEMPO/CuI synergetic catalyzed oxidative cross-coupling of indoles with benzylamines: Synthesis of bis(indolyl) phenylmethanes

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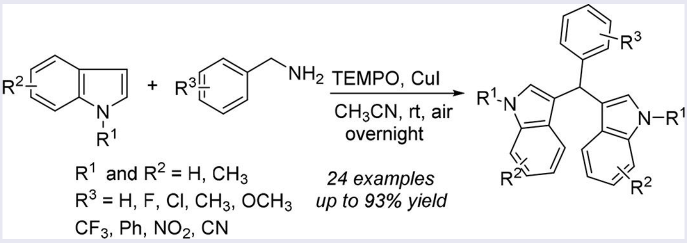
ABSTRACT
TEMPO/CuI was found to be an effective catalyst for the cross-coupling of indoles with benzylic amines affording the corresponding bis(indolyl)phenylmethanes under air atmosphere at room temperature in good to excellent yields. The efficiency, easy workup, simplicity, and chemoselectivity of this protocol provide a green and low-cost procedure for the synthesis of these compounds.

ARTICLE HISTORY
Received 12 February 2018

KEYWORDS
Benzylamine; bis(indolyl) methane; indole; TEMPO

GRAPHICAL ABSTRACT



Introduction

The bis(indolyl)alkane and their derivatives are present in various natural products possessing important biological activity,[1] such as antibacterial, antimicrobial, antibiotic, anticarcinogenic, genotoxicity, and DNA-damaging properties and are known to have applications in research areas such as pharmaceuticals and materials science.[2] Therefore, several synthetic methods for the preparation of bis(indolyl)alkane derivatives have been reported in the literature by reacting indoles with various aldehydes and ketones in the presence of either a Lewis acid[3] or a protic acid.[4] Metal triflates[5] such as Ln(OTf)$_3$, Dy(OTf)$_3$, In(OTf)$_3$, LiClO$_4$,[6] HClO$_4$,[7] and molecular iodine[8] have also been used for the synthesis of bis(indolyl)alkanes. However, these methods suffer from various drawbacks such as longer reaction times, use of expensive reagents, low yields, involvement of complicated purification processes Therefore, the development of simple and convenient

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Supplemental data (experimental procedures and ^{1}H and ^{13}C NMR data for all compounds) can be accessed on the publisher's website.

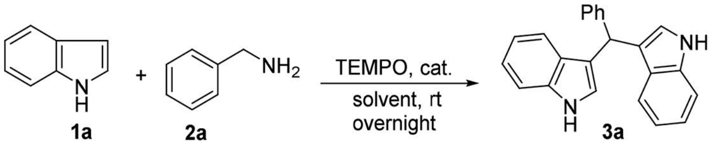
procedures for the synthesis of bis(indolyl)alkanes continues to be a challenging endeavor in synthetic organic chemistry.

The recent demand for highly efficient and environmentally benign syntheses of fine chemicals and pharmaceuticals has encouraged the development of mild, safe, and highly chemoselective catalysts. The persistent nitroxide TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl radical) and derivatives thereof are highly valuable organocatalysts for the conversion of primary and secondary alcohols to the corresponding carbonyl compounds.[9] The catalytically active species in most of these reactions is not the nitroxide itself, but its oxidized form, the corresponding *N*-oxo-ammonium salt. In practice, the oxoammonium salt is generated *in situ* by one-electron oxidation using various organic[10] or inorganic cooxidants.[11] As a result, dioxygen has been investigated as a terminal oxidant in nitroxide-based oxidation protocols.[12] Herein, we report a highly selective and efficient catalytic method for the oxidative cross-coupling of benzylic amines with indoles to synthesize bis(indolyl)phenylmethane derivatives using TEMPO as the oxidant, $Cu(OAc)_2$ as the catalyst, and molecular oxygen as the terminal oxidant under an O_2 atmosphere at room temperature.

Results and discussion

Our initial efforts were focused on the investigations with the reaction of indole **1a** with benzylic amine **2a** to search for the optimal reaction conditions. The results of these studies are listed in Table 1. In the first attempt, the reaction was catalyzed by TEMPO (10 mol%) in the presence of $CuSO_4$ (10 mol%) in CH_3CN at room temperature for overnight. To our

Table 1. Optimization of the reaction conditions[a].



Entry	TEMPO (mol%)	Metal (mol%)	Solvent	Isolated yield (%)[b]
1	10	$FeCl_3$ (10)	CH_3CN	6
2	10	$FeSO_4$ (10)	CH_3CN	9
3	10	$CoCl_2$ (10)	CH_3CN	5
4	10	$NiCl_2 \cdot 6H_2O$ (10)	CH_3CN	10
5	10	$LaCl_3 \cdot 7H_2O$ (10)	CH_3CN	5
6	10	$CuSO_4$ (10)	CH_3CN	56
7	10	CuO (10)	CH_3CN	43
8	10	Cu_2O (10)	CH_3CN	61
9	10	CuI (10)	CH_3CN	73
10	10	–	CH_3CN	Trace
11	5	CuI (10)	CH_3CN	52
12	15	CuI (10)	CH_3CN	86
13	20	CuI (10)	CH_3CN	85
14	–	CuI (10)	CH_3CN	0
15	15	CuI (10)	THF	77
16	15	CuI (10)	$CHCl_3$	69
17	15	CuI (10)	DMF	72
18	15	CuI (10)	Benzene	60

[a] The reaction conditions: indole (1.0 mmol) benzylic amine (0.6 mmol), metal catalyst (0.1 mmol) in 1 mL solvent at RT for overnight.

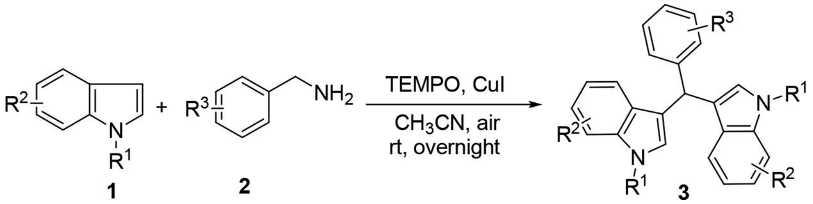
[b] Isolated yield based on indole **1a**.

delight, the expected product **3a** was isolated and obtained in 56% yield (Table 1, entry 6). Other metals, such as $FeCl_3$, $FeSO_4$, $CoCl_2$, $NiCl_2 \cdot 6H_2O$, and $LaCl_3 \cdot 7H_2O$, were examined subsequently (Table 1, entries 1–5), and copper catalyst was demonstrated to be the best choice. In light of this result, we decided to investigate this reaction with respect to copper sources, TEMPO loading, and solvent to achieve the optimal procedure. Evaluation of copper sources showed that CuI was the best choice in the transformation, affording the desired product **3a** in 73% yield (Table 1, entry 9). However, a trace amount of the targeted product was observed in a control experiment without the addition of metal salts.

We next examined the effect of TEMPO loading on the reaction, good result was obtained when using 15 mol% TEMPO (Table 1, entry 12), and there was no advantage to using more than 15 mol% TEMPO (Table 1, entry 13), whereas the yield significantly decreased when using only 5 mol% TEMPO (Table 1, entry 11). Control experiments confirmed that, without TEMPO catalyst, the formation of **3a** was not observed (Table 1, entry 14). After examining different solvents including acetonitrile, THF, $CHCl_3$, C_6H_6, and DMF, acetonitrile was found to be most efficient, with which the highest yield of 86% was obtained when using 15 mol% TEMPO and 10 mol% CuI at room temperature for overnight (Table 1, entry 12).

Having established the optimal reaction conditions, we wanted to investigate the scope of methodology for the various benzylic amines and indoles. The results are compiled in Table 2. Table 2 shows that various benzylic amines can react with substituted indoles to give the corresponding bis(indolyl)phenylmethanes **3** in good to excellent yields. Indoles can be unsubstituted indoles (Table 2, entries 1–9), *N*-CH_3 (Table 2, entries

Table 2. TEMPO/CuI-catalyzed reaction of benzylic amines with indoles[a].



Entry	Compound	R^1	R^2	R^3	Yield (%)[b]
1	**3a**	H	H	H	86
2	**3b**	H	H	4-F	89
3	**3c**	H	H	4-CH_3	81
4	**3d**	H	H	4-OCH_3	79
5	**3e**	H	H	4-CF_3	90
6	**3f**	H	H	4-Ph	80
7	**3g**	H	H	3-Cl	84
8	**3h**	H	H	3-CH_3	78
9	**3i**	H	H	3-OCH_3	75
10	**3j**	CH_3	H	H	89
11	**3k**	CH_3	H	3-Cl	86
12	**3l**	CH_3	H	3-OCH_3	82
13	**3m**	CH_3	H	3-NO_2	93
14	**3n**	CH_3	H	4-CN	90
15	**3o**	CH_3	H	4-CF_3	92
16	**3p**	H	2-CH_3	3-CH_3	83
17	**3q**	H	2-CH_3	3-OCH_3	78

[a] The reaction conditions: indole (1.0 mmol), benzylic amine (0.6 mmol), TEMPO (0.15 mmol), and CuI (0.1 mmol) in 1 mL CH_3CN at RT for overnight.

[b] Isolated yield based on **1**.

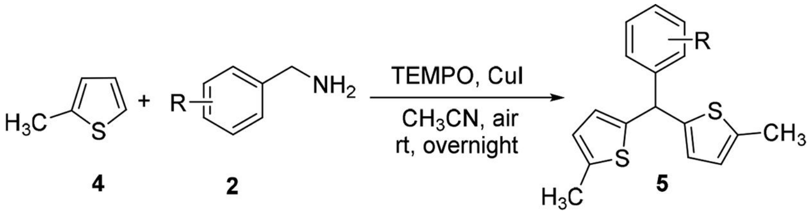
10–15), and 2-CH_3 (Table 2, entries 16 and 17). The results also have shown that substitution in the benzylamine played a major role in governing the reactivity of the substrate. With electron-donating substituents in the benzylamines, decreased yields of products were observed (Table 2, entries 3, 4, 6, 8, and 9). For example, the reaction of 3-methoxybenzyl amine with indole gave corresponding product **3i** in 75% yield (Table 2, entry 9). However, the effect was reversed when the electron-withdrawing group was present in the benzylamine. Electron-withdrawing groups (e.g., NO_2, CN, and CF_3) in the benzylamine favored the reaction with indoles, affording the corresponding bis(indolyl)phenylmethanes in high yields (Table 2, entries 5 and 13–15). It is noteworthy that the reaction of *N*-methyl indole with benzyl amines gave the corresponding bis(indolyl)phenylmethanes in slightly better yields (Table 2, entries 10–15).

To expand the scope of the protocol, the reaction of 2-methyl thiophene with various benzylamines was also evaluated. The results are summarized in Table 3. As shown in Table 3, good yields were obtained in CH_3CN at RT for overnight. Benzylamines with electron-donating substituents and with electron-withdrawing substituents were all well tolerant of the reaction conditions. Steric effect also had an adverse influence on the reaction. For instance, 2-bromo benzylamine gave a lower reaction yield of 67% (Table 3, entry 7).

To evaluate the practicability of our method, the reaction between indole **1a** (5.85 g, 50 mmol) and benzyl amine **2a** (3.22 g, 30 mmol) has been performed on a large scale in a single batch, and to our delight, no yield loss was observed with even lower initiator loading (10 mol% TEMPO/8 mol% CuI in 25 mL CH_3CN at room temperature, finished in 10 h, 88% isolated yield). That is to say, here we present a practical and scalable synthetic entry to the bis(indolyl)phenylmethanes.

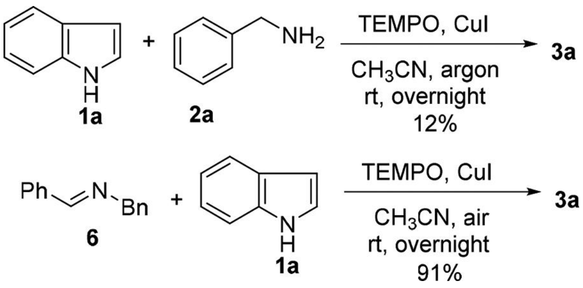
We further performed several control experiments under the standard conditions to probe the reaction mechanism. First, the reaction proceeded badly in argon instead of air (Scheme 1). Further, we attempted to treat **6** with indole (2 equiv.) **1a** under the standard conditions. Pleasingly, **6** and **1a** could smoothly be transformed into **3a** in 91%

Table 3. TEMPO/CuI-catalyzed reaction of benzylic amines with 2-methyl thiophene[a].

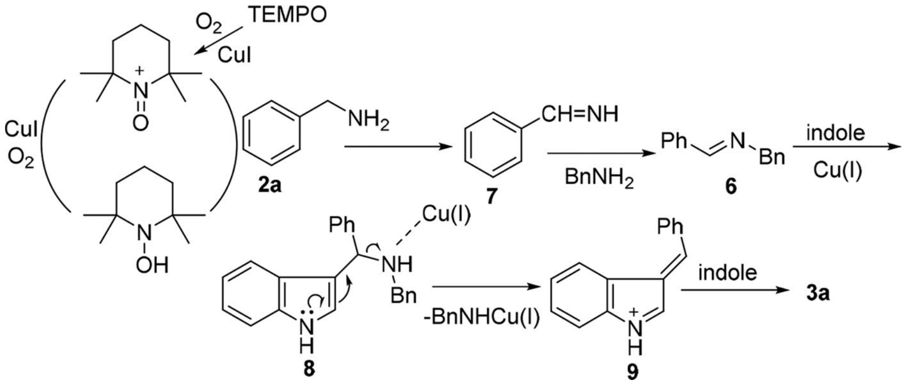


Entry	Compound	R	Yield (%)[b]
1	**5a**	H	82
2	**5b**	4-CH_3	77
3	**5c**	3-Cl	85
4	**5d**	3-CH_3	80
5	**5e**	3-OCH_3	73
6	**5f**	3-NO_2	93
7	**5g**	2-Br	67

[a]The reaction conditions: 2-methyl thiophene (1.0 mmol) and benzyl amine (0.6 mmol), TEMPO (0.15 mmol), and CuI (0.1 mmol) in 1 mL CH_3CN at RT for overnight.
[b]Isolated yield based on **4**.



Scheme 1. Control experiments.



Scheme 2. Proposed reaction pathway of TEMPO/CuI-catalyzed benzylamine with indole.

yield, suggesting that **6** might be an intermediate in this reaction and the reaction mechanism is similar to the iron-catalyzed oxidative coupling of benzylamines and indoles.[13b]

Based on the above experimental results and previous reports,[8,13] a plausible reaction pathway for the TEMPO/CuI-catalyzed benzylamine with indole is shown in Scheme 2. First, benzylamine was oxidized using TEMPO/CuI in air into imine **7**, which should be unstable and was transformed into corresponding imine **6** by reacting with another amine. Subsequently, **6** is activated by Cu(I), then performed a nucleophilic addition reaction at C-3 of indole to give mono(indolyl)phenylmethane **8**. After the elimination of BnNHCu(I), the intermediate **9** was generated. Finally, nucleophilic addition of indole **1a** to intermediate **9** gave the desired product **3a**.[5a,13,14]

Conclusion

In conclusion, we have demonstrated that the TEMPO/CuI is a highly efficient catalyst for the synthesis of 3,3′-bis(indolyl) phenylmethanes from indoles and benzylamines in high yields. The synthesis proceeds at room temperature without the requirement of inert or anhydrous reaction conditions. In addition, efficiency, easy workup, simplicity, and chemoselectivity of this protocol provide a green and low-cost procedure for the synthesis of these compounds.

Experimental section

General procedure for the preparation of bis(indolyl)phenylmethanes 3

To a solution of benzylamine (0.6 mmol), indole (1.0 mmol), and CuI (0.1 mmol) in CH_3CN (1 mL) was added TEMPO (0.15 mmol) under atmosphere and the mixture was stirred at room temperature for overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluant:EtOAc/PE = 1:4) to yield the corresponding product.

Funding

The authors are grateful to the Natural Science Foundation of Jiangxi Province (No: 20161BAB203096) for financial support.

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