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2-Aroylindoles from *o*-bromochalcones *via* Cu(I)-catalyzed S_NAr with an azide and intramolecular nitrene C–H insertion†

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A simple procedure for the synthesis of 2-aroylindole derivatives comprising a one-pot CuI-catalyzed S_NAr reaction of *o*-bromochalcones with sodium azide and subsequent intramolecular cyclization through nitrene C–H insertion has been developed. This protocol is also applicable with the 2′-bromocinnamates giving the indole-2-carboxylates.

Indole is one of the most commonly encountered heterocyclic units in a wide range of bioactive molecules.[1] The early disclosure of its constitution/structure in dealing with the synthesis of indigo, "indole synthesis", has witnessed a constant progress in its research during the last two centuries and has bagged several named reactions.[2,3] Indole derivatives having a carbonyl functional group at C2 are important building blocks for natural product/pharmacologically active compound synthesis, in particular C2–aroyl indole derivatives.[4] The C2–aroyl indole derivatives without any N- or C3 substituent have been identified as potent small molecular modulators for diverse biological targets such as cell surface receptors (receptor tyrosine kinase), nuclear receptor proteins, cyclooxygenase and histone deacetylases and have also proven to be important in controlling the polymerization of tubulin.[5] The examination of these derivatives across a wide range of biological targets was, in particular, possible because of their ready availability and because of the development of reliable protocols for their synthesis.[6–9]

The deoxygenation of β-substituted-*o*-nitrostyrenes with $P(OEt)_3$, trivially known as the "Cadogan–Sundberg indole synthesis" is one of the early methods in this direction, despite the fact that it afforded 2-ethoxycarbonyl- and 2-acylindoles in very poor yields.[7] The involvement of a singlet nitrene and its insertion across the C–H bond of the olefin unit is a generally accepted mechanism in these nitro-reduction processes.[8] Replacing the nitro with an azide as a nitrene surrogate has not seen much success when the reactions are conducted under standard pyrolysis or photolysis conditions.[9]

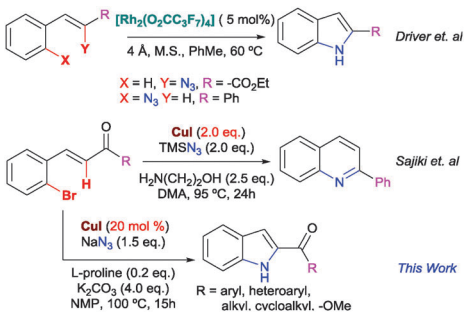

Fig. 1 Metal-catalyzed cyclization of azidostyrene derivatives.

Driver and co-workers have recently reported intramolecular C–H amination from either side *via* a Rh-catalyzed decomposition of α-azidoacrylates or aryl azides leading to indole derivatives.[10] Our group has been working on the Cu-catalyzed S_NAr of aryl halides with azide and the trapping of the intermediate azide either for cycloaddition or cyclization.[11] Given the current interest in 2-aroylindole synthesis, we speculated on the possibility of a one-pot [Cu]-catalysed synthesis of 2-aroylindoles from easily accessible *o*-bromochalcones (Fig. 1).[12,13]

Initial experiments with simple α-bromochalcone **1a** under the previously established conditions [20 mol% of each of $CuSO_4 \cdot 5H_2O$, sodium ascorbate and L-proline, 1.5 equivalents of K_2CO_3 and NaN_3 in DMSO at 80 °C for 15 h][11b] gave a mixture of the required 2-benzoylindole (**2a**, 47%), along with the 2-phenylquinoline (**3a**, 39%). Having obtained the first promising results, we next focussed on the optimization of the reaction conditions. As shown in Table 1, among the various copper sources employed, CuI was found to be the best for the present transformation.[13a] The outcome of the required 2-aroylindole increased by switching the solvent from DMSO, DMA to NMP (Table 1, entries 2–4). While the presence of Na-ascorbate is not essential, the presence of the base K_2CO_3 (4.0 equivalents) is required (Table 1 entry 8). However, other bases such as Cs_2CO_3 and Na_2CO_3 did not show any improvement in the yield (Table 1, entries 9 and 10). Reducing the concentration of the ligand L-proline from 100 mol%

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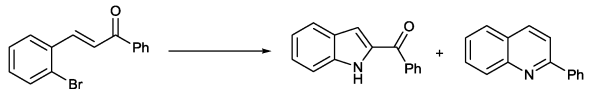
Table 1 Optimization of reaction condition[a]



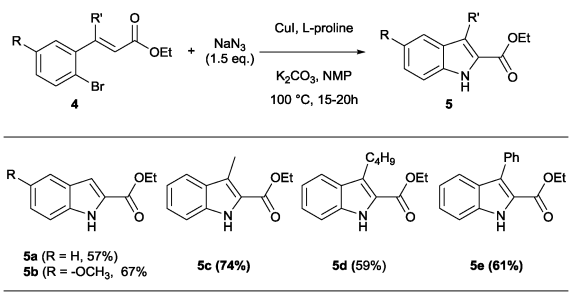
Sr. No	Catalyst	Solvent	Base	Yield (**2a**)[b,c,d] (%)	Yield (**3**)[b,c,d]
1	$CuSO_4$	DMSO	1.5	47[e]	39%[e]
2	CuI	DMSO	1.5	56	41%
3	CuI	DMA	1.5	62	38%
4	CuI	NMP	1.5	69	26%
5	CuI	NMP	—	47	13% (39%)[h]
6	CuI	NMP	2.0	80	20%
7	CuI	NMP	3.0	81	5% (4%)
8	CuI	NMP	4.0	86	3%
9	CuI	NMP	1.5[e]	49[f]	51%
10	CuI	NMP	3.0[f]	72[g]	27%
11	$CuSO_4$	NMP	1.5	52[e]	5% (27%)[e]
12	**CuI**	**NMP**	**4.0**	**87**	**1%**
13	CuI	NMP	3.0	75	7% (17%)
14	CuCl	NMP	4.0	84	— (4%)
15	Cu_2O	NMP	3.0	54	24% (21%)
16	—	NMP	4.0	ND	ND

[a] Reaction condition: *o*-bromochalcone (**1a**, 1 eq.), NaN_3 (1.5 eq.), CuI (20 mol%), L-proline (0.2 eq.), K_2CO_3 (4.0 eq.) in NMP at 100 °C for 15 h. [b] L-Proline (1.0 eq.) was used for entries 2–11. [c] Yield based on GC. [d] Isolated yield. [e] (20 mol%) Na-ascorbate was used. [f] Cs_2CO_3 used as a base. [g] K_2CO_3 use as base. [h] Parenthesis indicate (%) starting intact.

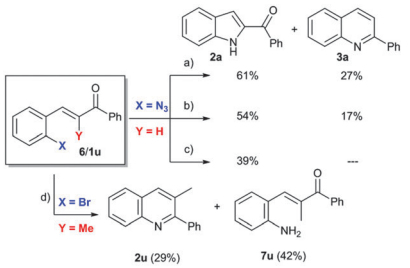
to 20 mol% did not show any effect on the reaction efficiency (Table 1, entry 12).

The generality of the current reaction has been examined first by selecting the substrates where the nature of substituent next to the carbonyl has been varied from aromatic to heteroaromatic, cycloalkyl and alkyl groups. The reactions with other aromatic/heterocyclic rings like naphthyl, furyl, pyrrol, pyridine, benzofuran and benzothiophene gave the desired products in moderate to good yields. However, when the aryl ring was replaced by an alkyl or cyclopropyl group, the yields were seen to decrease. Next, the scope of the present reaction was further extended by employing 2-bromochalcones having different substituents on both the phenyl rings. The substituents on the bromoaryl ring do not have much influence on the reaction outcome. On the other hand, with substrates having the electron donating group on the aryl ring next to the carbonyl, the reaction yields are moderate (Scheme 1).

To look at the compatibility of an ester group, the *o*-bromocinnamate and the 2-bromo-5-methoxy cinnamate have been subjected to the current reaction and the corresponding indoles **5a** and **5b** respectively were obtained in good yields.



Scheme 1 Cu(I)-catalyzed synthesis of indole-2-carboxylates.

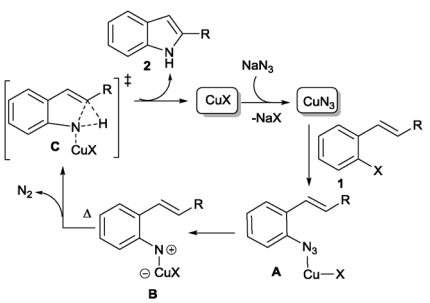


Scheme 2 *Reagents and conditions*: (a) CuI (20 mol%), L-proline (20 mol%), K_2CO_3 (4.0 eq.) in NMP at 100 °C, for 15 h; (b) CuI (20 mol%), NMP at 100 °C for 15 h; (c) NMP at 100 °C for 15 h; (d) same as condition (a) along with NaN_3 (1.5 eq.).

These experiments revealed that the carboxylate group can be a suitable alternative for the aroyl group. The suitability of the C3-substituted *o*-bromocinnamates (prepared by the two-carbon Wittig homologation of the corresponding ketones) as substrates has been examined next. As shown in Scheme 2. The one-pot S_NAr-cyclization reaction of *o*-bromocinnamates **4c–4e** having respectively, the methyl, butyl, or phenyl group at C3 proceeded smoothly to afford the corresponding indole-2-carboxylates **5c–5e** in good yields (Scheme 2).

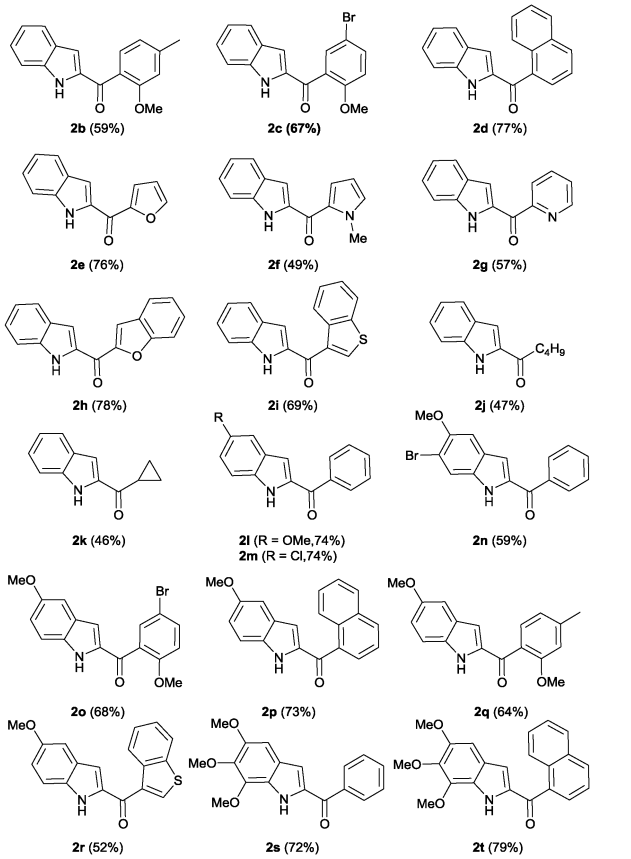
To understand the course of the reaction, control experiments were conducted with the 2-azidochalcone **6** and with the bromochalcone **1u** having a methyl group in place of the hydrogen atom to be abstracted. As shown in Scheme 3, the treatment of 2-azidochalcone **6** with CuI under optimized conditions resulted in a mixture of indole **2a** and quinolone **3a** derivatives. A similar result was obtained when the reaction was conducted only with 20 mol% CuI and without any other additive. On the other hand, when **6** was heated alone in NMP, it gave exclusively indole in 39% yield. However, the reaction of the *o*-bromochalcone **1u** with a C2–methyl substituent under standard conditions resulted in the formation of a mixture of quinolone **3u** and the aniline derivative **8**. These results clearly indicate that while the involvement of a nitrene-intermediate essentially leads to indole formation, when the copper salt is present, the yields are better, indicating the possible involvement of a copper–nitrenoid species. However, the reduction of the aryl azide seems to be a competing process at high azide concentrations (Table 2).

With the available information in hand and considering the previous reports,[14] we propose the following tentative mechanism. Earlier it has been shown that the [Cu] is required for the S_NAr with



Scheme 3 Plausible catalytic cycle.

Table 2 Scope of the [Cu]-catalyzed 2-aroyl indole synthesis



azide and that the decomposition of the azide takes place after the aryl azide formation.[13,14c,15] There exist two possibilities for the subsequent C–N bond formation.[8,16] A step-wise process involving an initial C–N bond formation and subsequent C–H bond cleavage,[8,10a,16] or a concerted process[10a,13a] with simultaneous breaking of the C–H bond and the formation of the C–N bond. Considering the fact that the reacting olefin in the present case is electron deficient and that the chalcone **1u** having a 2-methyl substituent did not provide any indole derivative (the formation of which is expected due to the migration of the methyl group if it is a step-wise process)[10a] we propose that a concerted process is operating in the present case, having Cu-participation in both the steps (Scheme 3).

In conclusion, a simple catalytic protocol for the preparation of 2-aroylindoles from 2-bromochalcones has been developed. This Cu-catalyzed process involves a set of three reactions – (i) S_NAr with azide and (ii) conversion of azide to nitrene; and (iii) intramolecular insertion of nitrene across the C–H bond – with the net formation of two new C–N bonds.

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Notes and references

1 (*a*) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620; (*b*) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694; (*c*) S. Biswal, U. Sahoo, S. Sethy, H. K. S. Kumar and M. Banerjee, *Asian J. Pharm. Clin. Res.*, 2012, **5**, 1.

2 (*a*) A. Baeyer and A. Emmerling, *Ber. Dtsch. Chem. Ges.*, 1869, **2**, 679; (*b*) A. Baeyer, *Justus Liebigs Ann. Chem.*, 1866, **140**, 295.

3 (*a*) M. Inman and C. J. Moody, *Chem. Sci.*, 2013, **4**, 29; (*b*) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev.*, 2012, **41**, 3929; (*c*) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641; (*d*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (*e*) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045.

4 (*a*) G. A. Tunbridge, J. Oram and L. Caggiano, *Med. Chem. Commun.*, 2013, **4**, 1452; (*b*) E. Yamuna, R. A. Kumar, M. Zeller and K. J. Rajendra Prasad, *Eur. J. Med. Chem.*, 2012, **47**, 228; (*c*) M. A. Tarselli, K. M. Raehal, A. K. Brasher, J. M. Streicher, C. E. Groer, M. D. Cameron, L. M. Bohn and G. C. Micalizio, *Nat. Chem.*, 2011, **3**, 449; (*d*) L. You, Z. Xu, C. Punchihewa, D. M. Jablons and N. Fujii, *Mol. Cancer Ther.*, 2008, **7**, 1633; (*e*) S. G. Abdel-Moty, A. M. Abdel-Aal, A. N. Kafafy and A. A. El-Shorbagi, *Bull. Pharm. Sci., Assiut Univ.*, 2005, **28**, 213; (*f*) R. Leurs, P. L. Chazot, F. C. Shenton, H. D. Lim and I. J. P. De Esch, *Br. J. Pharmacol.*, 2009, **157**, 14.

5 (*a*) A. Brancale and R. Silvestri, *Med. Res. Rev.*, 2007, **27**, 209; (*b*) S. Mahboobi, A. Sellmer, H. Hocher, C. Garhammer, H. Pongratz, T. Maier, T. Ciossek and T. Beckers, *J. Med. Chem.*, 2007, **50**, 4405; (*c*) S. Mahboobi, S. Teller, H. Pongratz, H. Hufsky, A. Sellmer, A. Botzki, A. Uecker, T. Beckers, S. Baasner, C. Schachtele, F. Uberall, M. U. Kassack, S. Dove and F. D. Bohmer, *J. Med. Chem.*, 2002, **45**, 1002; (*d*) T. M. Willson, P. J. Brown, D. D. Sternbach and B. R. Henke, *J. Med. Chem.*, 2000, **43**, 527.

6 Selected examples: (*a*) B. V. S. Reddy, M. R. Reddy, Y. G. Rao, J. S. Yadav and B. Sridhar, *Org. Lett.*, 2013, **15**, 464; (*b*) W.-C. Gao, S. Jiang, R.-L. Wang and C. Zhang, *Chem. Commun.*, 2013, **49**, 4890; (*c*) C. Pan, H. Jin, X. Liu, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 2933; (*d*) B. Zhou, Y. Yang and Y. Li, *Chem. Commun.*, 2012, **48**, 5163; (*e*) Q.-Q. Yang, C. Xiao, L.-Q. Lu, J. An, F. Tan, B.-J. Li and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 9137; (*f*) Y. Zhao, D. Li, L. Zhao and J. Zhang, *Synthesis*, 2011, 873; (*g*) E. C. Creencia, M. Kosaka, T. Muramatsu, M. Kobayashi, T. Iizuka and T. Horaguchi, *J. Heterocycl. Chem.*, 2009, **46**, 1309; (*h*) M. Arthuis, R. Pontikis and J.-C. Florent, *Org. Lett.*, 2009, **11**, 4608; (*i*) D. S. C. Black and L. C. H. Wong, *J. Chem. Soc., Chem. Commun.*, 1980, 200; (*j*) C. D. Jones and T. Suarez, *J. Org. Chem.*, 1972, **37**, 3622.

7 (*a*) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie and R. J. G. Searle, *J. Chem. Soc.*, 1965, 4831; (*b*) R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604.

8 P. A. S. Smith, C. D. Rowe and D. W. Hansen Jr, *Tetrahedron Lett.*, 1983, **24**, 5169.

9 (*a*) K. Samiran and L. Saswati, *J. Indian Chem. Soc.*, 1999, 607; (*b*) E. T. Pelkey and G. W. Gribble, *Tetrahedron Lett.*, 1997, **38**, 5603; (*c*) R. J. Sundberg, H. F. Russell, W. V. Ligon and L.-S. Lin, *J. Org. Chem.*, 1972, **37**, 719.

10 (*a*) M. Shen, B. E. Leslie and T. G. Driver, *Angew. Chem., Int. Ed.*, 2008, **47**, 5056; (*b*) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500.

11 (*a*) C. V. Ramana, Y. Goriya, K. A. Durugkar, S. Chatterjee, S. Krishnaswamy and R. G. Gonnade, *CrystEngComm*, 2013, **15**, 5283; (*b*) Y. Goriya and C. V. Ramana, *Chem. Commun.*, 2013, **49**, 6376.

12 T. Maejima, Y. Shimoda, K. Nozaki, S. Mori, Y. Sawama, Y. Monguchi and H. Sajiki, *Tetrahedron*, 2012, **68**, 1712.

13 (*a*) Y. Ou and N. Jiao, *Chem. Commun.*, 2013, **49**, 3473; (*b*) Y. Goriya and C. V. Ramana, *Tetrahedron*, 2010, **66**, 7642.

14 (*a*) Y. Naruta, N. Nagai, Y. Arita and K. Maruyama, *J. Org. Chem.*, 1987, **52**, 3956; (*b*) P. Dauban, L. Saniere, A. Tarrade and R. H. Dodd, *J. Am. Chem. Soc.*, 2001, **123**, 7707; (*c*) M. R. Kumar, A. Park, N. Park and S. Lee, *Org. Lett.*, 2011, **13**, 3542.

15 W. Zhu and D. Ma, *Chem. Commun.*, 2004, 888.

16 Z. Shi, Y. Ren, B. Li, S. Lu and W. Zhang, *Chem. Commun.*, 2010, **46**, 3973.

