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Synthesis of 3-[2-(1,3-butadienyl)]-1*H*-indoles en route to murrapanine analogue

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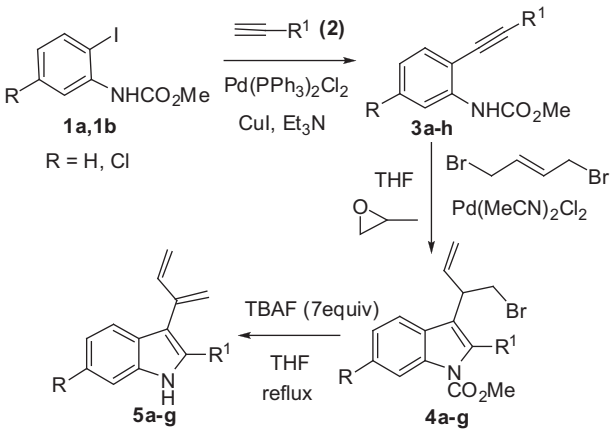
ABSTRACT

A three-step procedure has been developed for the synthesis of 3-[2-(1,3-butadienyl)]-1*H*-indoles. TBAF was proved to be an effective reagent for dehydrobromination and carbomethoxy deprotection in one step to give 3-[2-(1,3-butadienyl)]-1*H*-indoles from the corresponding bromo-derivatives. Suitably substituted indolyl-1,3-butadiene has been successfully applied to prepare murrapanine analogue via Diels–Alder reaction.

The indole nucleus is a prominent structural motif found in numerous biologically active natural products[1] and synthetic compounds with vital medicinal value. Therefore, assembly of functionalized indoles has captured the attention of synthetic chemists for decades and continues to be an active research area.[1a,2] In continuation of our research effort directed towards discovering new indole scaffolds for medicinal application and indole alkaloids synthesis, we sought to prepare 3-[2-(1,3-butadienyl)]-1*H*-indoles in which the 2-position of the indole ring is suitably substituted.

Upon examination of the literature, we were surprised that there is no report on the synthesis of 3-[2-(1,3-butadienyl)]-1*H*-indoles though a few reports are available on the synthesis of 3-[1-(1,3-butadienyl)]-1*H*-indoles.[3] The literature also revealed that alkaloids having a (3-indolyl)-planar system as a structural feature shows important biological activities.[4] The indole-substituted dienes could serve as a precursor for the synthesis of these alkaloids and their analogues. Prompted by these studies, we wish to disclose a methodology for the synthesis of such dienes using dehydrobromination and carbomethoxy deprotection in one step mediated by TBAF (Scheme 1) and application of such dienes towards the synthesis of Diels–Alder adducts including the synthesis of murrapanine analogue.

Our synthesis commenced with the formation of *o*-alkynylanilines (**3a–3j**) (Table 1). Thus, a series of terminal acetylenes (**2a–2h**) were reacted with methyl carbamate protected iodoanilines (**1a and 1b**) in the presence of CuI (5 mol %) and $Pd(PPh_3)_2Cl_2$ (2.5 mol %) in Et_3N and afforded *o*-alkynylanilines (**3a–3h**) in moderate to excellent yields. Under the same condition, the acetylenes **2i** and **2j** did not undergo Sonogashira coupling reactions. Hence, **3i** and **3j** were synthesized using modified Sonogashira conditions in moderate to fair yields.[5] For the preparation of **3i**, bearing a CO_2Et group on the alkynyl moiety, the Sonogashira reaction was carried out using Na_2CO_3 as a base replacing triethyl amine under heating conditions in dioxane–water mixture. Compound **3j** was prepared by the coupling between 2-bromothiophene and 2-ethynylaniline followed by carbomethoxy protection of aromatic amine.



Scheme 1. Synthesis of butadiene-substituted indoles.

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Table 1
Synthesis of acetylenes (**3a**–**3j**)

Entry	R	R^1	Time (h)	Product[b]	Yield[a] (%)
1	H	C_6H_5	12	**3a**	84
2	H	4-$CH_3C_6H_4$	12	**3b**	80
3	H	*n*-C_3H_7	8	**3c**	76
4	H	C_6H_{11}	10	**3d**	83
5	H	CH_2OH	7	**3e**	69
6	H	CH_2CH_2OH	8	**3f**	69
7	Cl	C_6H_5	12	**3g**	86
8	H	2-$NO_2C_6H_4$	5	**3h**	55
9	H	CO_2Et	0.5	**3i**[c]	35
10	H	2-Thiophene	14	**3j**[d]	75

[a] Isolated yield.
[b] Reactions were carried out at room temperature using 1.2 equiv of alkyne.
[c,d] Refs. 5a,b were followed.

We next turned our attention to the synthesis of 2,3 -disubstituted indoles (**4a–4j**), in which the 3-position of the indole ring is substituted with homoallyl bromide. Surprisingly, only one report[6] was available on the synthesis of such indole derivatives and no spectral data were reported regarding the stereochemistry of the allyl moieties. Therefore, we tried this reaction following the report by Utimoto et al.[6] for the installation of homoallyl bromide in the 3-position of indoles by way of palladium catalysis. Accordingly, **3a** was reacted with trans 1,4-dibromobut-2-ene (3.5 equiv) to get the desired product **4a** in the presence of $Pd(MeCN)_2Cl_2$ (5 mol %), and propylene oxide was used as a proton scavenger. Applying this method, several other indole derivatives (**4b**–**4g**) were prepared and the results are summarized in Table 2. Unfortunately, alkynylanilines **3h** and **3i** did not undergo the reaction and the starting materials were recovered. In case of **3j**, a trace amount of carbomethoxy-protected 2-thiophene indole was obtained. The spectral data revealed that there is no incorporation of homoallyl bromide at the 3-position of the indole ring.

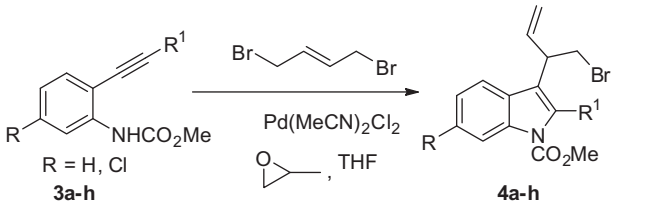
Alkynylanilines (**3a–3c**), **3g** and **3l** reacted smoothly with trans 1,4-dibromo-2-butene at room temperature and afforded the corresponding 2,3-disubstituted indoles in moderate to good yields. Compound **3l** was synthesized by routine functional group transformations from compound **3f**. On the other hand, the reaction with alkynylanilines **3d** and **3k** (THP protected form of **3e**) was very sluggish at room temperature and afforded 2,3-disubstituted indoles in very poor yields (10%). However, refluxing the reaction mixture provided the disubstituted indoles **4d** and **4e** in 45% and 46% yields, respectively. The yields did not improve even after prolonged heating.

Having secured access to a range of 2,3-disubstituted indoles, we began our studies by evaluating the effect of different bases on dehydrobromination and carbomethoxy deprotection in a single step using **4a** as a standard substrate (Table 3).

To optimize the reaction condition, when compound **4a** was treated with methanolic KOH,[7] a mixture of undetermined products was obtained. Thus we decided to carry out the dehydrobromination and carbomethoxy deprotection in stepwise fashion. Accordingly, when different bases like Et_3N, DIPEA and DBU were tested to carry out the dehydrobromination reaction, no desired product was obtained. In case of NaH, a trace amount of dehydrohalogenated product **6a** was obtained. Further addition of NaH and increase of reaction temperature was ineffective to improve the yield of product **6a**. In order to increase the yield, we decided to enhance the acidity of alpha hydrogen adjacent to the 3-position of the indole ring, thus facilitating the dehydrobromination reaction. We envisioned that replacement of methylcarbamate with more electron withdrawing group like tosyl might enhance the acidity of that alpha hydrogen. Primarily, we examined K_2CO_3, TMSI and LiOH to deprotect the carbomethoxy group, but only in the case of LiOH, we obtained a trace amount of deprotected product. Interestingly, when the reaction mixture was heated to reflux in the presence of TBAF[8] (5 equiv), we observed a mixture of products containing **5a** and **6a**, where diene **5a** was the major product. We realized that under this reaction condition, dehydrobromination is more facile than carbomethoxy deprotection. Accordingly, we became intrigued by the possibility that increasing the amount of TBAF might offer a straightforward approach to the synthesis of 3-[2-(1,3-butadienyl)]-1*H*-indole derivatives in one pot. To our delight, using TBAF (7 equiv) ultimately provided the desired indolyl butadiene **5a** in 71% yield.

With the optimized condition, we next evaluated the substrate scope of this reaction. Several 2,3-disubstituted indoles (**4a–4g**) were successfully reacted with TBAF to give the corresponding indolyl butadiene derivatives (**5a–5e**) and **5g** in good to excellent yields (Table 4). This reaction is tolerant to a variety of substituents on the indole ring. It is noteworthy that compound **4f** underwent

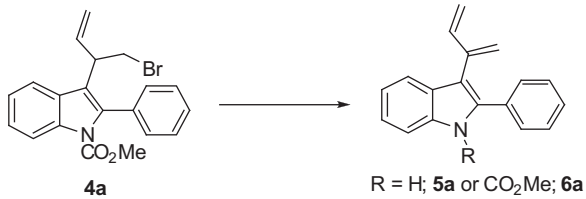
Table 2
Synthesis of 2,3-disubstituted indoles



Entry	Substrate (**3**)	R^1	Temp (°C)	Time (h)	Product (**4**)	Yield[a] (%)
1	**3a**	C_6H_5	25	5	**4a**	51
2	**3b**	4-$CH_3C_6H_4$	25	5	**4b**	51
3	**3c**	*n*-C_3H_7	25	5	**4c**	56
4	**3d**	C_6H_{11}	66	2.5	**4d**	45
5	**3g**[b]	C_6H_5	25	5	**4g**	71
6	**3h**[c]	2-$NO_2C_6H_4$	66	5	**4h**	0
7	**3i**[c]	CO_2Et	66	12	**4i**	0
8	**3j**	2-Thiophene	66	12	**4j**	0
9	**3k**	CH_2OTHP	66	2.5	**4e**	46
10	**3l**	CH_2CH_2NHBoc	25	5	**4f**	50

[a] Isolated yield.
[b] R = Cl.
[c] Starting material was recovered.

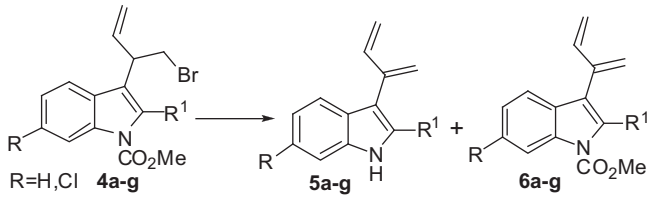
Table 3
Optimization of the reaction conditions



Base	Equiv	Solvent	Temp (°C)	Time (h)	Yield[a,b] (%)	
					5a	**6a**
KOH	1.5	MeOH	25	1	0	0
Et_3N	1.5	THF	66	10	nr[c]	
DIPEA	1.5	THF	66	10	nr[c]	
DPU	1.5	DMF	60	1.5	0	0
NaH	1.5	THF	25	8	Trace	
NaH	3	THF	25	8	Trace	
NaH	3	THF	66	5	Trace	
TBAF	5	THF	66	2.5	43	12
TBAF	7	THF	66	2.5	71	0

[a] Isolated yield.
[b] All the reactions were carried out in 1 mmol scale.
[c] No conversion was observed.

Table 4
Synthesis of 3-[2-(1,3-butadienyl)]-1*H*-indoles



Entry	Substrate (**4**)	R^1	Product[b]	Yield[a] (%)	
				5	**6**
1	**4a**	C_6H_5	**5a**	71	0
2	**4b**	4-$CH_3C_6H_4$	**5b**	91[c]	0
3	**4c**	*n*-C_3H_7	**5c**	66	0
4	**4d**	C_6H_{11}	**5d**	60	0
5	**4e**	CH_2OTHP	**5e**	62	0
6	**4f**	CH_2CH_2NHBoc	**6f**	0	63[d]
7	**4g**[e]	C_6H_5	**5g**	73	0

[a] Isolated yield.
[b] Reaction mixture was stirred for 2 h.
[c] Reaction time was 3.5 h.
[d] 1.5 equiv NaH was used and stirred for 1.5 h.
[e] R = Cl.

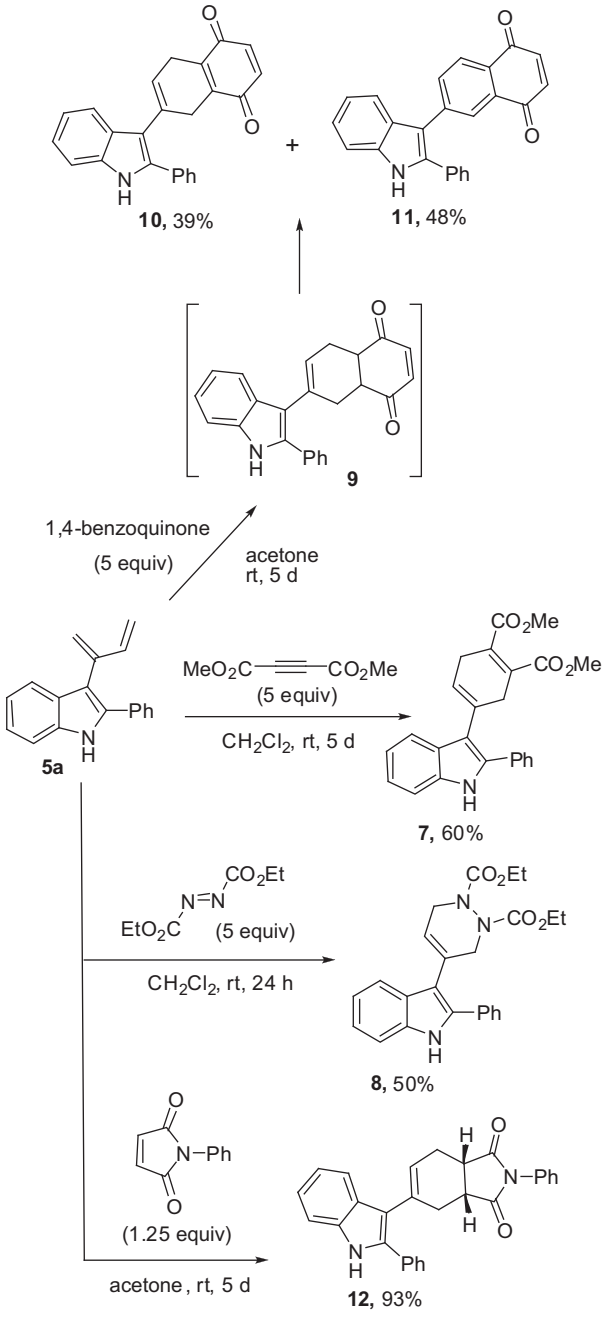
Boc deprotection with TBAF, thereby resulted in a free amine and no eliminated product was obtained. When **4f** was treated with NaH, diene **6f** was obtained in 63% yield, presumably due to the fact that initial deprotonation from NHBoc, followed by abstraction of the alpha hydrogen was beneficial for dehydrobromination.

Next we were interested in exploring further possibilities for the assembly of diverse indole-containing skeletons which could have potential applications in medicinal chemistry. Accordingly, indolyl butadiene **5a** was used for the Diels–Alder reaction against the dienophiles DMAD, DEAD, *N*-phenylmaleimide and 1,4-benzoquinone and we were pleased to obtain moderate to good yields of the Diels–Alder adducts[4a] (Scheme 2). The Diels–Alder reaction was very slow at room temperature. Attempts to improve it by heating the reaction mixture in toluene or THF failed to give the desired product and the starting material was also decomposed. We figured out that when the reactions were carried out in dark, better yields were obtained. In the presence of light, butadiene was not very stable[4a] and the product was obtained in very poor yield along with the isolation of an undetermined product.

In the case of Diels–Alder reaction of indolyl butadiene **5a** with 1,4-benzoquinone, we obtained a mixture of products containing almost an equal amount of 6-(2-phenyl-1*H*-indol-3-yl)naphthalene-1,4(5*H*,8*H*)-dione (**10**) and 6-(2-phenyl-1*H*-indol-3-yl)naphthalene-1,4-dione (**11**). The formation of the aromatized product **11** was possible by the oxidation of cycloadduct **9** by the presence of excess *p*-benzoquinone as was expected. This observation was rationalized from the HRMS data obtained after 24 h stirring of the reaction mixture. Cycloadduct **11** is an analogue of alkaloid murrapanine which has cytotoxicity against cancer cells, particularly demethoxymurrapanines are more cytotoxic than murrapanines[9] (Fig. 1).

The reaction of **5a** and *N*-phenymaleimide gave rise to a single diastereomer cycloadduct **12** with an excellent yield. The stereochemistry of the adduct was determined by X-ray crystallography,[10,11] which reveals that cycloaddition occurred on the *endo* face of the diene (Fig. 2).

In conclusion, we have developed a method for the synthesis of suitably substituted 3-[2-(1,3-butadienyl)]-1*H*-indoles[12] in overall good yields starting from **3a–3g** with the easily available reagents. To the best of our knowledge, this is the first report for the synthesis of such indolyl butadiene derivatives. Moreover, the synthetic usefulness of such diene derivatives has been demonstrated in the preparation of murrapanine analogue. Further studies using these dienes to synthesize indole alkaloids and diverse indole scaffolds are currently underway and results will be reported in due course.



Scheme 2. Diels–Alder reaction of indolyl butadiene **5a**.

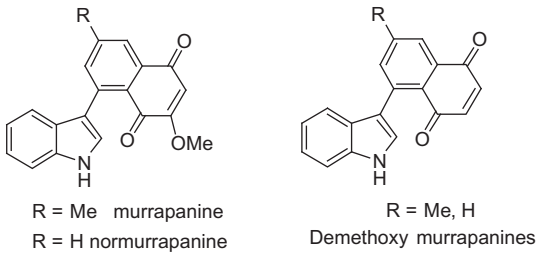


Figure 1. Structure of murrapanine and analogues.

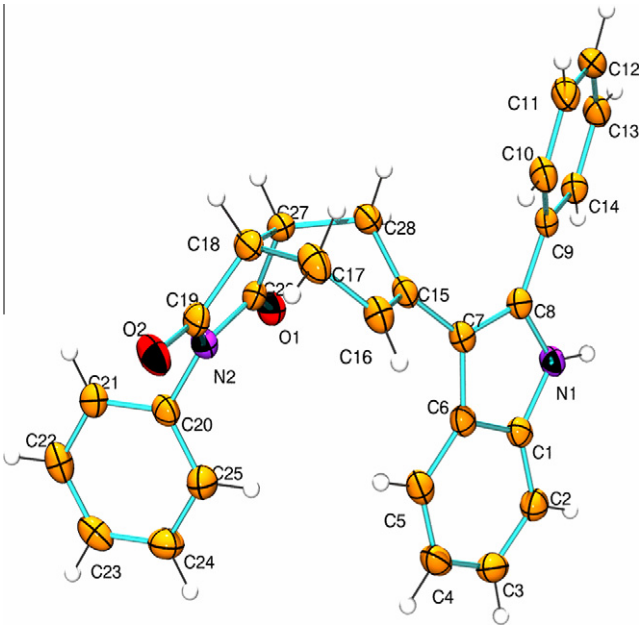


Figure 2. Thermal ellipsoid plot of compound **12** with thermal ellipsoid drawn at 50% probability level.

Acknowledgments

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Supplementary data

Supplementary data (general procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.003.

References and notes

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11. X-ray crystallographic data for compound **12** have been deposited to the Cambridge Crystallographic Data Centre and assigned the deposition numbers CCDC 837675 for **12**.
12. *General procedure for the synthesis of 3-[2-(1,3-butadienyl)]-1H-indoles* **5**: To a solution of *N*-carbomethoxy-2,3-disubstituted indole **4** (0.5 mmol) in anhydrous THF (5 mL) was added TBAF (3.5 mmol) under argon atmosphere and the reaction mixture was heated to reflux for 1.5–2.5 h (reaction was monitored by TLC), cooled to room temperature and the crude mixture was diluted with ethyl acetate (15 mL), washed twice with saturated NH_4Cl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate in petroleum ether to afford pure indolyldienes **5** in good to excellent yields Table 4.
Characterization data for the compound **5a** is given below:
Yellow crystalline solid. Mp 105–107 °C. IR (KBr) ν 3398, 3082, 3059, 3026, 2997, 2970, 1595, 1450, 1487, 1450, 1415, 1361, 1325, 1301, 1284, 1224, 1147, 1030, 1003, 985, 898, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24 (s, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 3H),7.33–7.30 (m, 1H), 7.23 (t, J = 6.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.69 (dd, J = 17, 10.5 Hz, 1H), 5.58 (d, J = 2 Hz 1H), 5.28 (s, 1H), 5.08 (d, J = 10 Hz, 1H), 5.02 (d, J = 17 Hz, 1H),; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.7, 138.4, 135.9, 134.5, 132.9, 129.7, 128.8 (2C), 127.7, 127.3 (2C), 122.7, 120.6, 120.2, 120.2, 117.2, 112.5, 110.8; High resolution MS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{16}N$: 246.1283, found: 246.1276.