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Synthesis of isoxazolobenzoxepanes via Michael addition of indoles to nitroalkenes and sequential intramolecular nitrile oxide cycloaddition

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ABSTRACT

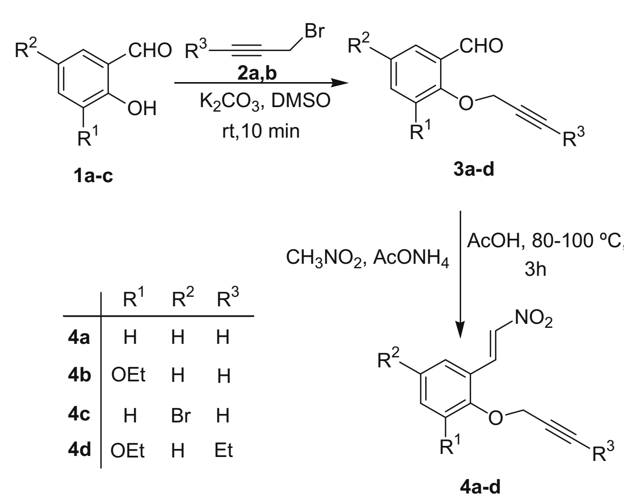
Nitroalkenes derived from *O*-propargyl salicylaldehyde undergo facile Michael addition with indoles leading to indole-derived Michael adducts. Intramolecular nitrile oxide cycloaddition (INOC) of the Michael adducts results in isoxazolobenzoxepanes in good to excellent yields.

Nitrogen and oxygen containing heterocycles are ubiquitous substructures in a myriad of biologically active natural products and small-molecule pharmaceuticals.[1,2] The nitrile oxide cycloaddition is a useful method to prepare heterocyclic compounds.[3,4] Isoxazole, the cycloadduct of nitrile oxide, is regarded as a versatile synthetic precursor for γ-amino alcohols and β-hydroxy ketones. There have been many examples applying the present methodology to the preparation of five- or six-membered carbo- and heterocyclic compounds[5] as well as the preparation of medium- or large-sized cyclic compounds.[6,7]

Nitrile oxides are readily generated through various methods such as dehydration of primary nitro compounds[8] or oxidative treatment of oximes.[9] Intramolecular nitrile oxide cycloaddition (INOC) offers a powerful strategy to construct carbo- or heterocyclic compounds and many reports on the stereoselective INOC reaction have been published in recent years.[10] Nitroalkenes have been known as a good Michael acceptor and widely used in organic synthesis.[11] Conjugate addition to a nitroalkene and subsequent generation of a nitrile oxide is frequently applied to achieve a successful INOC reaction.[12]

In continuation of our work with 1,3-dipolar cycloadditions,[13] we herein report the facile synthesis of isoxazolobenzoxepanes by INOC. The preparation of INOC precursors **6** was carried out by the Michael addition of indoles with nitroalkenes[14] (Scheme 1) in the presence of $KHSO_4$ in water[15] (Scheme 2). The Michael addition reaction was completed within 3–5 h at room temperature and the corresponding adducts **6** were isolated by column chromatography. For example, the treatment of the 1-ethoxy-3-(2-nitrovinyl)-2-(prop-2-ynyloxy)benzene (**4b**) with *N*-ethylindole (**5c**) in $KHSO_4/H_2O$ medium resulted in the formation of adduct **6h** in 89% yield. The Michael addition product **6h** was confirmed through NMR and mass spectral studies.[16]

Initial studies of INOC were carried out using Michael adduct **6h** as a model substrate with phenyl isocyanate and Et_3N in CH_3CN at 60 °C (Scheme 3). The reaction yielded a single product **7h**, which was isolated by column chromatography (Table 1, entry 1). The



Scheme 1. Preparation of nitroalkenes **4**.

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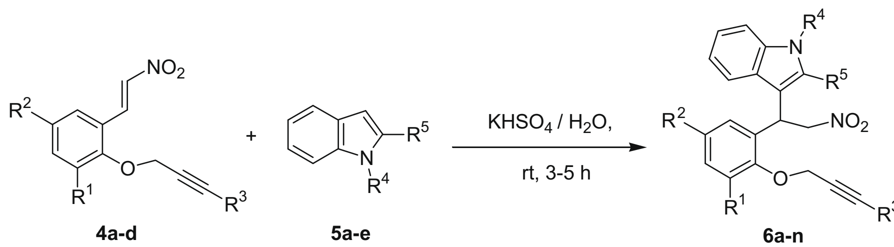
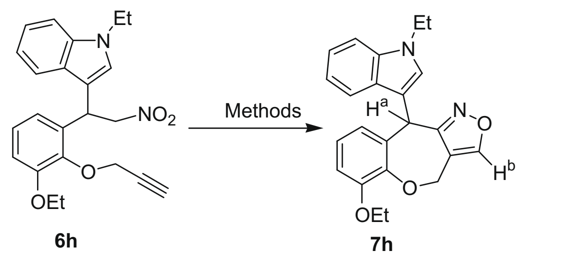
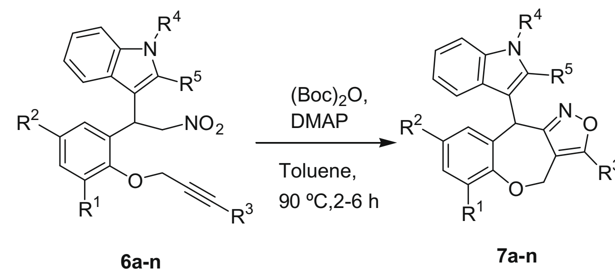


Scheme 2. Michael addition of indoles to nitroalkenes.



Scheme 3. Synthesis of isoxazolobenzoxepane (**7h**) by different methods.



Scheme 4. Synthesis of isoxazolobenzoxepanes (**7a**–**n**).

Table 1
Methods to generate nitrile oxide and sequential INOC (**7h**)

Entry	Methods	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	PhNCO, Et_3N	CH_3CN	60	12	20
2		CH_2Cl_2	40	24	35
3		THF	60	24	Trace
4		Toluene	90	24	42
5	EtOCOCl, Et_3N, DMAP	CH_3CN	90	12	38
6		CH_2Cl_2	40	12	Trace
7		THF	60	12	10
8		Toluene	90	24	52
9	$(Boc)_2O$, DMAP	CH_3CN	60	8	40
10		CH_2Cl_2	40	12	48
11		THF	60	12	26
12		Toluene	60	4	74
13		Toluene	90	2	92

[a] Isolated yield after column chromatography.

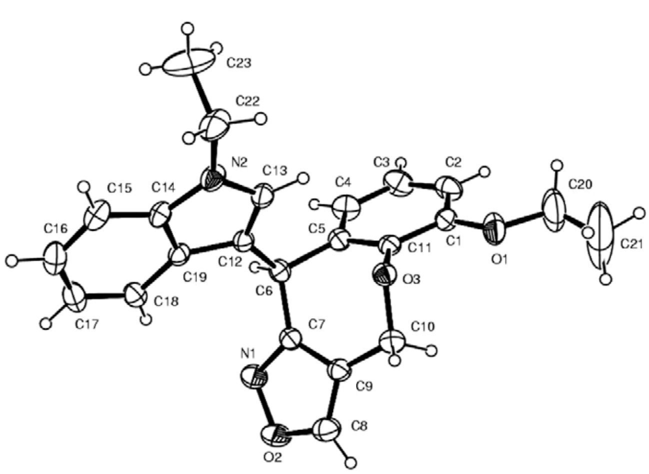


Figure 1. ORTEP diagram of compound **7h**.

structure was confirmed by NMR and mass spectral studies.[17] In ^1H NMR spectrum of the compound **7h**, the two doublet of doublets at δ 4.94 (J = 14.5, 1.9 Hz) and 5.24 (J = 14.5, 1.5 Hz) ppm were assigned to $-OCH_2$ protons. The two singlets at δ 5.82 and 8.08 ppm were attributed to H^a and H^b protons, respectively. The mass spectrum revealed the molecular ion peak $[M+H]^+$ at m/z 375. The structure was further confirmed by X-ray crystallographic analysis of the compound **7h** (Fig. 1).[18]

Having obtained the isoxazolobenzoxepane product, we next varied the reaction conditions in order to increase the yield of the products from its initial low yield of 20%. Change of solvent from CH_3CN to CH_2Cl_2, THF and toluene moderately increased the yield up to 42% (Table 1, entries 2–4). Then we changed the reaction conditions from phenyl isocyanate/Et_3N to ethyl chloroformate/Et_3N and DMAP and $(Boc)_2O$/DMAP, the yield increased moderately (Table 1, entries 5–12). When toluene was used as a solvent at 90 °C in $(Boc)_2O$/DMAP method the yield was maximum (up to 92%) (Table 1, entry 13).

Under the above optimized condition the reaction of various substituted Michael adducts **6a–n** was examined and the corresponding isoxazolobenzoxepane derivatives **7a–n** were obtained in good yields (Scheme 4, Table 2). After these encouraging results, we modified the *O*-propargyl group with an internal alkyne instead of a terminal alkyne moiety to examine the feasibility and yield of the reaction, but only a small variation was observed.

The additional advantage of this method is the use of di-*tert*-butyl dicarbonate which allows the reaction to be carried out with substrates that contain –*N*H groups without requiring protecting groups, thus the cycloaddition leads to *N*-Boc products. For example, cycloaddition of 2-methyl-3-{2-nitro-1-[2-(prop-2-ynyloxy)phenyl]ethyl}-1*H*-indole (**6b**) with $(Boc)_2O$ and DMAP affords the *N*-Boc protected indolyl substituted isoxazolobenzoxepane **7b** in 85% yield (Table 2, entry 2).

In summary, we have reported the Michael addition of indoles to β-nitrostyrenes possessing *O*-propargyloxy groups to generate nitroalkanes and the use of $(Boc)_2O$, in combination with DMAP to convert the nitroalkanes into nitrile oxide to undergo intramolecular nitrile oxide-alkyne cycloaddition (INOC) to form isoxazolobenzoxepane. A study on the application of this method to synthesize novel heterocyclic compound by using different nucleophiles is underway.

Table 2
Synthesis of isoxazolobenzoxepanes (**7a–n**)

Entry	Nitro alkenes **4**	Indoles **5**			Michael adducts **6**	Yield[a] (%)	Cycloadducts **7**	Time (h)	Yield[a] (%)
		R^4	R^5						
1	**4a**	Me	H	**5a**	**6a**	90	**7a**	2.0	96
2	**4a**	H	Me	**5b**	**6b**	85	**7b**	2.0	85
3	**4a**	Et	H	**5c**	**6c**	92	**7c**	2.5	92
4	**4a**	Bn	H	**5d**	**6d**	60	**7d**	5.0	83
5	**4a**	*p*-Br–Bn	H	**5e**	**6e**	55	**7e**	6.0	75
6	**4b**	Me	H	**5a**	**6f**	91	**7f**	3.5	92
7	**4b**	H	Me	**5b**	**6g**	88	**7g**	3.0	90
8	**4b**	Et	H	**5c**	**6h**	89	**7h**	2.5	92
9	**4b**	Bn	H	**5d**	**6i**	64	**7i**	5.5	80
10	**4b**	*p*-Br–Bn	H	**5e**	**6j**	59	**7j**	6.0	72
11	**4d**	Me	H	**5a**	**6k**	92	**7k**	3.0	86
12	**4c**	Me	H	**5a**	**6l**	90	**7l**	2.5	85
13	**4c**	H	Me	**5b**	**6m**	84	**7m**	3.5	91
14	**4c**	Et	H	**5c**	**6n**	86	**7n**	3.0	87

[a] Isolated yield after column chromatography.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.001.

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16. *Representative experimental procedure for the synthesis of nitroalkane* (**6h**): To the nitroalkene **4b** (1.74 mmol) in water (10 mL) was added $KHSO_4$ (30 mol %) and the mixture was stirred for 5 min. *N*-Ethylindole **5c** (1.74 mmol) was added to the mixture and the stirring was continued following the progress of the reaction by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and the residue was column chromatographed over silica gel using EtOAc/Petroleum ether (1.5:8.5) as eluent to get the pure product (**6h**).
3-{1-[3-Ethoxy-2-(prop-2-ynyloxy)phenyl]-2-nitroethyl}-1-ethyl-1H-indole (**6h**): Colourless solid; mp 95–97 °C; R_f = 0.28 (20% ethylacetate/petroleum ether); IR (cm^{-1}): 1551, 1376, 1461, 2162, 3282, 2976; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43–1.48 (m, 6H), 2.49 (t, 1H, J = 2.3 Hz), 4.06 (q, 2H, J = 6.9 Hz) 4.13 (q, 2H, J = 6.8 Hz), 4.72 (dd, 1H, J = 15.3, 2.3 Hz), 4.84 (dd, 1H, J = 15.3, 2.3 Hz), 5.02–5.10 (m, 2H), 5.69 (dd, 1H, J = 9.2, 6.9 Hz), 6.79–6.82 (m, 2H), 6.96 (t, 1H, J = 7.6 Hz), 7.03–7.06 (m, 2H), 7.19 (t, 1H, J = 8.4 Hz), 7.30 (d, 1H, J = 8.4 Hz), 7.55 (d, 1H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 15.6, 36.1, 41.1, 59.9, 64.3, 75.6, 78.5, 79.7, 109.5, 112.5, 112.6, 119.2, 119.7, 120.5, 121.9, 124.6, 124.8, 127.2, 133.6, 136.2, 144.7, 152.1; ESI-MS (LCQ) m/z = 393 $[M+H]^+$; Anal. Calcd for $C_{23}H_{24}N_2O_4$ (392.17): C, 70.39; H, 6.16; N, 7.14. Found: C, 70.45; H, 6.14; N, 7.17.
17. *Representative experimental procedure for the synthesis of isoxazolobenzoxepane* (**7h**): The nitroalkanes (1.0 mmol) **6h** and DMAP (0.2 mmol) were dissolved in toluene (5 mL). Di-*tert*-butyl dicarbonate (2.5 mmol) in toluene (5 mL) was added in portions over a period of 0.5 h at 90 °C to the nitroalkanes solution

and the reaction was allowed to proceed for a further 2 h. The mixture was evaporated and the product was purified by column chromatography using EtOAc/Petroleum ether (2:8) as eluent.

8-Ethoxy-4-(1-ethyl-1H-indol-3-yl)-4H,10H-2,9-dioxa-3-azabenzo[f]azulene (**7h**): Colourless solid; mp 158–160 °C; R_f = 0.24 (20% ethylacetate/petroleum ether); IR (cm^{-1}): 1265, 1472, 1594, 2978, 3220; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (t, 3H, J = 6.8 Hz), 1.48 (t, 3H, J = 6.8 Hz), 4.05–4.16 (m, 4H), 4.94 (dd, 1H, J = 14.5, 1.9 Hz), 5.24 (dd, 1H, J = 14.5, 1.5 Hz), 5.82 (s, 1H), 6.91 (d, 1H, J = 7.6 Hz), 6.96–6.97 (m, 1H), 7.04–7.09 (m, 2H), 7.04–7.09 (m, 1H), 7.17 (t, 1H, J = 6.9 Hz), 7.27 (t, 1H, J = 8.4 Hz), 7.77 (d, 1H, J = 7.6 Hz), 8.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 15.6, 38.9, 41.1, 64.3, 64.4, 109.3, 112.8, 112.9, 116.3, 119.1, 119.7, 121.4, 121.6, 125.4, 126.6, 127.2, 135.9, 136.5, 145.9, 152.4 152.8, 161.5; ESI-MS (LCQ) m/z = 375 [M+H]$^+$; Anal. Calcd for $C_{23}H_{22}N_2O_3$ (374.16): C, 73.78; H, 5.92; N, 7.48. Found: C, 73.87; H, 5.96; N, 7.37.

18. Crystallographic data of compound **7h** in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplemental publication No. CCDC-764294. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).