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Intramolecular [3+2] nitrile oxide cycloaddition: synthesis of tetrahydroisoxazoloindazoles

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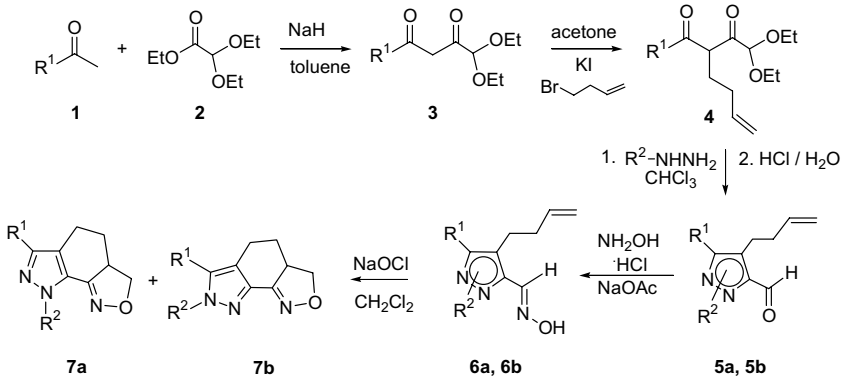
Abstract—Novel tetrahydroisoxazoloindazoles were synthesized from substituted 1,3-diketones by employing intramolecular [3+2] nitrile oxide cycloaddition [INOC] reaction to alkene as the key step.

Among a great number of heterocycles, pyrazoles[1] and isoxazolines[2] are especially important motifs used not only as key building blocks for the synthesis of their derivatives in medicinal chemistry, but also as invaluable chelating ligands for various transition metals. While pyrazole derivatives, including celecox,[3] have been the most important drugs as of today, the isoxazoline nucleus not only provides its derivatives with a variety of biological activities but also modulates various other biologically active motifs.[4] Although there are numerous reports for the synthesis of both pyrazoles and isoxazolines, few routes to construct fused ring systems with each heterocycle tethered together in the same molecule are known.[5] Those activities mentioned above, coupled with our program focusing on potential biological and/or metal chelating ligands, led us to explore a synthetic pathway to construct novel tetrahydroisoxazoloindazoles, pyrazole-isoxazoline heterocycle about central carbocyclic cores. The most common method to construct pyrazole heterocycles involves the reaction of 1,3-diketones or their equivalents with substituted hydrazines.[6] Meanwhile isoxazolines are normally synthesized by employing a 1,3-dipolar cycloaddition reaction of a nitrile oxide to an alkene.[7] Thus, we designed the route to our fused tetrahydroisoxazoloindazole heterocycles to include intramolecular nitrile oxide cycloaddition (INOC) as the key step, as depicted in Scheme 1. We began our studies by preparing acetal



Scheme 1.

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protected diketone[8] **3** (60–68% yield) from the reaction of alkylmethylketone **1** with ethyl diethoxyacetate **2**, followed by C-alkylation of compound **3** to give homoallylated diketone **4** in good yield (74–90%). The subsequent reaction of compound **4** with hydrazine derivatives, followed by deprotection of acetal, afforded aldehyde **5**. As expected, when substituted hydrazine such as methylhydrazine ($R^2 = Me$) was used, aldehydes with a regioisomeric mixture (thus the regioisomer **5a** is corresponding to both **6a** and **7a**) were obtained.

Unfortunately remarkable regioselectivity was not observed regardless of the degree of bulkiness of the substituent R^1. To generate nitrile oxide, we employed oxime derivative as a precursor to the 1,3-dipole (Husgin method).[9] Thus each aldehyde **5** was condensed with hydroxylamine hydrochloride to afford oxime derivative **6** (79–98%) as a precursor to in situ generated nitrile oxide. Finally tetrahydroisoxazoloindazole **7** was obtained from the cycloaddition of nitrile oxide to the homoallyl group present in the oxime derivative **6** (Table 1).[10] As for the unsubstituted tetrahydroisoxazoloindazole **7** ($R^2 = H$), X-ray crystallography of the compound **7-1** ($R^1 = Me$, $R^2 = H$) showed that it exists as the tautomer **7b** and packed in a trimeric form through hydrogen bonding (Fig. 1). The regiochemistry of compound **7** ($R^2 = Me$) was also established by X-ray crystallographic analysis of either isomeric compound **7a** or **7b**.[10] For example the X-ray structure of compound **7-4a** ($R^1 = Me$, $R^2 = H$) is illustrated in Figure 2. Our attempt to make 5-5-5 ring system (pyrazole–cyclopentane–isoxazoline) as shown in compound **8** did not work by this route, most likely because of severe ring strain (Scheme 2).

In summary, we have developed a synthetic strategy for the preparation of novel heterocycles of tetrahydroisoxazoloindazole **7**. The work reported here secures our program aimed at both the development of novel ligand for various metals and/or the discovery of new pharmacophore through the structural diversification of the prepared tetrahydroisoxazoloindazole system.

Table 1. Examples of various tetrahydroisoxazoloindazoles **7** and their starting materials **5**

Compound **7** (yield[a] %)	R^1	R^2	Compound **5** (yield[b] %)
7-1 (51)	Me	H	**5-1** (83)
7-2 (77)	*t*-Bu	H	**5-2** (69)
7-3 (53)	Ph	H	**5-3** (52)
7-4a (74)	Me	Me	**5-4a** (55)
7-4b (85)	Me	Me	**5-4b** (15)
7-5a (81)	*t*-Bu	Me	**5-5a** (57)
7-5b (77)	*t*-Bu	Me	**5-5b** (20)
7-6a (88)	Ph	Me	**5-6a** (17)
7-6b (80)	Ph	Me	**5-6b** (53)

[a] Yield from compound **6**.
[b] Yield from compound **4**.

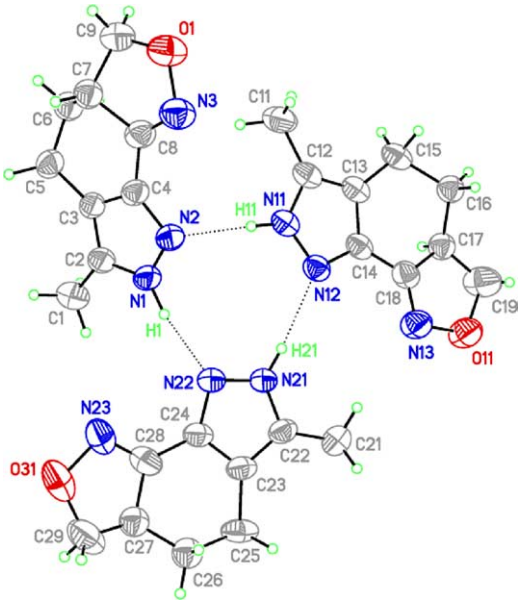


Figure 1. X-ray crystallography of compound **7-1** ($R^1 = Me$, $R^2 = H$), disordered positions removed for clarity. Thermal ellipsoids drawn to the 50% probability level.

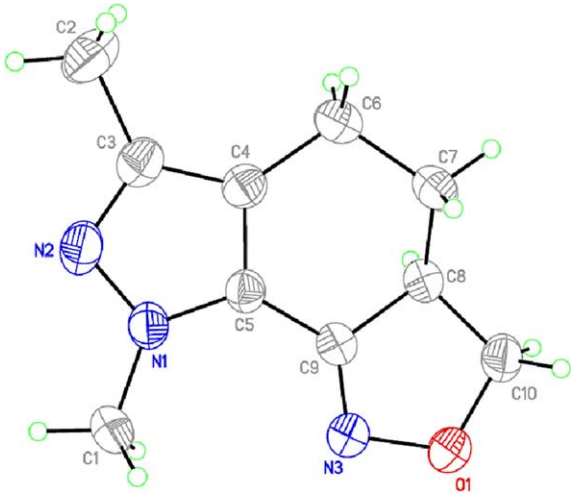
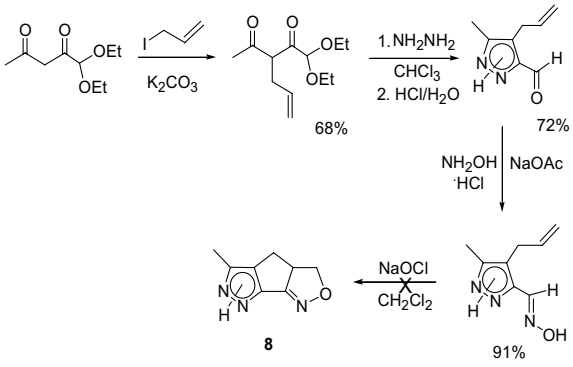


Figure 2. X-ray crystallography of compound **7-4a** ($R^1 = Me$, $R^2 = Me$), disordered positions removed for clarity. Thermal ellipsoids drawn to the 50% probability level.



Scheme 2.

Acknowledgements

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10. Representative procedure: 4-Bromo-1-butene (20 g, 148 mmol) was treated with KI (24.6 g, 148 mmol) in acetone (200 mL) by reflux overnight. The reaction mixture was filtered, then the filtrate was treated with compound **3** ($R^1 = Me$, 23 g, 122 mmol) in the presence of K_2CO_3 (20 g, 148 mmol) by overnight reflux. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure, followed by vacuum distillation (90 °C, 150 mTorr) to afford 22 g of compound **4** ($R^1 = Me$, 74%) as a liquid. Compound **4** ($R^1 = Me$, 11 g, 45.3 mmol) was reacted with hydrazine hydrate (4.15 g, 45.3 mmol, 35%) in chloroform (80 mL) at rt overnight. The organic layer was separated, and then concentrated under reduced pressure. The residue was treated with 1 N HCl (20 mL) in water (100 mL), then the resultant mixture was stirred at rt for 6 h. The precipitated white solid was filtered, and the filter cake was washed with saturated $NaHCO_3$ solution, then water successively. The solid was dried under a vacuum to afford compound **5-1** ($R^1 = Me$, $R^2 = H$, 6.2 g, 83%), then 6 g (36.5 mmol) of which was reacted with hydroxylamine hydrochloride (5.1 g, 73 mmol) in the presence of NaOAc (9 g, 109 mmol) in THF/MeOH/H_2O (100 mL/50 mL/50 mL) at rt overnight. After adding water (100 mL) to the reaction mixture, the reaction mixture was extracted with methylenechloride (80 mL × 2). The combined organic layer was washed with saturated $NaHCO_3$, dried (Na_2CO_3), then concentrated under reduced pressure. The resultant solid was washed with hexane to afford 6 g compound **6-1** ($R^1 = Me$, $R^2 = H$, 6 g, 92%). Finally to the solution of oxime (**6-1**, 5 g, 27.89 mmol) in CH_2Cl_2 (100 mL) was slowly added bleach (41 g, 33.47 mmol, 6.15%) dropwise at −10 °C. After stirring at rt for 5 h, the reaction mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated under reduced pressure. By column chromatography (70% ethyl acetate in hexane), compound **7-1** (2.51 g, 51%) was obtained as a white solid. **7-1** 51% yield; mp: 190 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, br, 1H), 4.74 (dd, 1H, $J = 9.5, 7.8$ Hz), 3.80 (dd, 1H, $J = 13.9, 7.8$ Hz), 3.54 (m, 1H), 2.75 (ddd, 1H, $J = 1, 7, 5.1, 15.9$ Hz), 2.59 (ddd, 1H, $J = 5.2, 12.5, 15.9$ Hz), 2.34 (m, 1H), 1.73 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 141.7, 133.4, 119.8, 73.5, 48.4, 28.0, 20.0, 10.7. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.88; H, 5.98; N, 23.58. Crystal data: $C_{27}H_{33}N_9O_3$, from hexane/ethyl acetate, colorless, irregular block, $\sim 0.360 \times 0.300 \times 0.260$ mm, monoclinic, P21/c, $a = 7.7566(8)$ Å, $b = 25.485(3)$ Å, $c = 13.4743(14)$ Å, beta = 100.578(2)°, Vol = 2618.3(5) Å^3, $Z = 4$, $T = -100$ °C, formula weight = 531.62, density = 1.349 g/cm^3, μ (Mo) = 0.09 mm^{-1} **7-2** 77% yield; mp: 223 °C ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, br, 1H), 4.72 (dd, 1H, $J = 8.0, 9.7$ Hz), 3.78 (dd, 1H, $J = 8.0, 13.6$ Hz), 3.52 (m, 1H), 3.00 (ddd, 1H, $J = 2.0, 5.3, 16.1$ Hz), 2.72 (ddd, 1H, $J = 5.0, 12.7, 16.1$ Hz), 2.34 m, 1H), 1.75 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.2, 153.1, 150.1, 146.6, 138.5, 128.4, 118.3, 115.5, 72.6, 72.3, 47.9, 47.3, 32.6, 32.4, 31.5, 30.6, 29.4, 27.8, 21.8, 21.2. M.W calcd for $C_{12}H_{17}N_3O$: 219.14, LC-MS $[M+H]^+ = 220.2$. **7-3** 53% yield; mp: 221 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.68 (m, 2H), 7.48–7.45 (m, 2H), 7.40–7.37 (m, 1H), 5.10 (s, br, 1H), 4.77 (dd, 1H, $J = 7.9, 9.1$ Hz), 3.82 (dd, 1H, $J = 7.9, 13.6$ Hz), 3.62 (m, 1H), 3.06 (ddd, 1H, $J = 1.6, 5.2, 16.2$ Hz), 2.93 (ddd, 1H, $J = 5.0, 12.6, 16.2$ Hz), 2.42 (m, 1H), 1.77 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.9, 149.9, 147.5, 139.2, 138.0, 133.3, 129.1, 128.9, 128.4, 127.9, 127.3, 126.2, 126.0, 119.4, 117.5, 72.6, 72.4, 47.9, 47.2, 27.6, 27.5, 21.4, 20.8. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.97; H, 5.51; N, 17.47. **7-4a** 74% yield; mp: 122 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (dd, 1H, $J = 8.1, 9.5$ Hz), 4.03 (s, 3H), 3.74 (dd, 1H, $J = 8.1, 14.0$ Hz), 3.50 (m, 1H), 2.73 (ddd, 1H, $J = 2.0, 5.4, 16.0$ Hz), 2.58 (ddd, 1H, $J = 4.8, 12.5, 16.0$ Hz), 2.33 (m, 1H), 2.21 (s, 3H), 1.69 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 144.9, 128.9, 120.9, 73.1, 48.8, 38.4, 27.8, 20.4, 11.6. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.94; H, 6.87; N, 22.03. Crystal data: $C_{10}H_{13}N_3O$, from hexane/ethyl acetate, colorless, irregular block, $\sim 0.520 \times 0.500 \times 0.450$ mm, orthorhombic, Pbcn, $a = 13.6524(17)$ Å, $b = 8.9306(11)$ Å, $c = 32.005(4)$ Å, Vol = 3902.2(8) Å^3, $Z = 16$, $T = -100$ °C, formula weight = 191.23, density = 1.302 g/cm^3, μ (Mo) = 0.09 mm^{-1} **7-4b** 85% yield; mp: 133 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 4.59 (dd, 1H, $J = 7.8, 9.5$ Hz), 3.76 (s, 3H), 3.65 (dd, 1H, $J = 7.8, 13.7$ Hz), 3.43 (m, 1H), 2.61 (ddd, 1H, $J = 1.7, 5.1, 15.7$ Hz), 2.47 (ddd, 1H, $J = 4.7, 13.0, 15.7$ Hz), 2.24 (m, 1H), 2.15 (s, 3H), 1.59 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 136.1, 134.3, 118.1, 72.1, 47.9, 35.7, 27.1, 19.2, 8.7. M.W calcd for $C_{10}H_{13}N_3O$; 191.1, LC-MS $[M+H]^+ = 192.1$. **7-5a** 81% yield; mp: 147 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (dd, 1H, $J = 8.1, 9.6$ Hz), 4.03 (s, 3H), 3.72 (dd, 1H, $J = 8.1, 14.4$ Hz), 3.44 (m, 1H), 2.99 (ddd, 1H, $J = 1.8, 5.1, 16.0$ Hz), 2.70 (ddd, 1H, $J = 4.9, 12.6, 16.0$ Hz), 2.25 (m, 1H), 1.65 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 151.0, 129.5, 119.0, 73.2, 48.5, 38.5, 33.0, 29.7, 28.1, 22.7. Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H,

8.21; N, 18.01. Found: C, 67.16; H, 8.02; N, 17.97. Crystal data: $C_{13}H_{19}N_3O$, from hexane/ethyl acetate, colorless, irregular block, $\sim 0.230 \times 0.230 \times 0.200$ mm, monoclinic, P21/c, $a = 9.6755(11)$ Å, $b = 10.4034(12)$ Å, $c = 12.8949(15)$ Å, beta = 105.542(2)°, Vol = 1250.5(2) Å^3, $Z = 4$, $T = -100$ °C, formula weight = 233.31, density = 1.239 g/cm^3, μ (Mo) = 0.08 mm^{-1} **7-5b** 77% yield; mp: 176 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (dd, 1H, $J = 8.0$, 9.8 Hz), 4.02 (s, 3H), 3.71 (dd, 1H, $J = 8.0$, 13.0 Hz), 3.41 (m, 1H), 3.03 (ddd, 1H, $J = 1.9$, 4.9, 16.1 Hz), 2.66 (ddd, 1H, $J = 4.8$, 12.9, 16.1 Hz), 2.25 (m, 1H), 1.65 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 146.1, 137.2, 117.6, 73.4 ,47.9, 41.3, 33.1, 30.5, 28.5, 23.5. Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.09; H, 8.06; N, 18.16. **7-6a** 88% yield; mp: 152 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.70 (m, 2H), 7.46–7.43 (m, 2H), 7.37–7.35 (m, 1H), 4.76 (dd, 1H, $J = 8.1$, 9.2 Hz), 4.18 (s, 3H), 3.79 (dd, 1H, $J = 8.1$, 13.8 Hz), 3.60 (m, 1H), 3.06 (ddd, 1H, $J = 1.9$, 5.0, 16.1 Hz), 2.92 (ddd, 1H, $J = 4.7$, 11.9, 16.1 Hz), 2.40 (m, 1H), 1.76 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 147.8, 133.1, 129.9, 128.6, 127.7, 126.8, 120.1, 73.3, 48.6, 39.0, 28.0, 22.3. Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.07; H, 5.81; N, 16.74. **7-6b** 80% yield; mp: 201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.42 (m, 3H), 7.33–7.32 (m, 2H), 4.69 (dd, 1H, $J = 7.9$, 9.5 Hz), 3.87 (s, 3H), 3.75 (dd, 1H, $J = 7.9$, 13.7 Hz), 3.56 (m, 1H), 2.66 (m, 2H), 2.28 (m, 1H), 1.69 (m,1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 140.3, 137.7, 129.4, 129.2, 128.9, 119.9, 73.3, 48.8, 37.9, 28.2, 20.9. Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.92; H, 5.77; N, 16.64. Crystal data: $C_{15}H_{15}N_3O$, from hexane/ether, colorless, prism, $\sim 0.250 \times 0.200 \times 0.120$ mm, monoclinic, P21/c, $a = 7.2409(15)$ Å, $b = 9.633(2)$ Å, $c = 17.930(4)$ Å, beta = 96.381(4)°, Vol = 1242.9(5) Å^3, $Z = 4$, $T = -100$ °C, formula weight = 253.30, density = 1.354 g/cm^3, μ (Mo) = 0.09 mm^{-1}.