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Convenient Synthesis of (1*H*)-Isoindoles and Cyclopenta[c]pyrrole Skeletons

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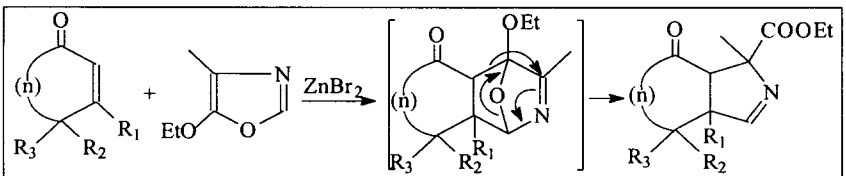
Abstract: *Diels-Alder reactions of various α, β-unsaturated cycloalkenones with 4-methyl-5-ethoxy-oxazole in the presence of $ZnBr_2$ provide hydro-(1H)- isoindoles and hydrocyclopenta[c]pyrrole.*

The first naturally occurring isoindole (2, 5-dimethyl-6-methoxy- 4, 7-dihydroisoindole- 4, 7-dione) was isolated from sponge *Reniera SP.*[1] Isoindole derivatives have been found useful as intermediates, for Substance P antagonists, and their preparation is of current interest.[2,3] Although isoindoles were first prepared in 1951, this area of chemistry received very limited attention in the literature until 1969. However, since 1970 considerable attention has been focused on their preparation and several synthetic routes have been reported. Prominent among them are intermolecular as well as intramolecular Diels-Alder reactions,[4] 1, 3-dipolar cycloaddition,[5] reaction of *o*-phthaldehyde with potassium cyanide and methylamine hydrochloride[6] and cyclization of 3, 4 - bisbromoacetyl-pyrrole.[7] Recently multistep new tandem ring contraction-autoxidation strategy for perhydrocyclopenta[c]pyrrole has been reported.[2]

Oxazoles have been extensively used as azadienes in cycloadditions, particularly for the synthesis of pyridine derivatives.[8] Continuing our studies on the synthetic utility of 4, 4-dimethyl-cyclohexenones,[9] we report herein a one pot synthesis of di-,tetra-,hexahydro -(1*H*) isoindoles and hexahydrocyclopenta[c]pyrrole



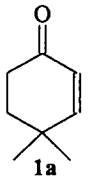
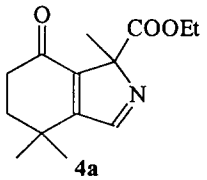
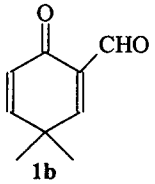
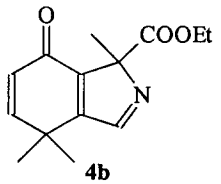
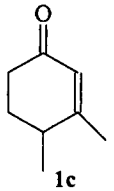
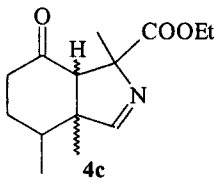
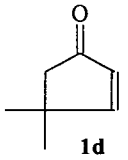
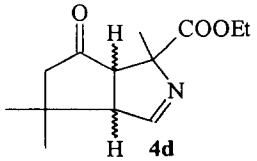
1a-d **2** **Scheme 1.** **3** **4a-d**

of type 4 through Diels-Alder reaction between cycloalkenones (**1a-d**) and oxazole (**2**)[10] (**Scheme 1**). The initial Diels-Alder adduct **3** which is known to be acid sensitive[8,11] undergoes subsequent rearrangement in the presence of $ZnBr_2$ to give the observed products **4a-d** (Table 1).

A mixture of dienophile (**1a-d,** 1mmol), 4-methyl-5-ethoxyoxazole (**2,** 1mmol) and a catalytic amount of anhydrous $ZnBr_2$ (10% by weight) was heated in benzene for the period described in Table-1, to yield the corresponding 1-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydro-1,4,4-trimethyl-(1*H*)-isoindole(**4a**),1-ethoxycarbonyl-4,7-dihydro-7-oxo-1,4,4-trimethyl-(1*H*)-isoindole (**4b**), 1-ethoxycarbonyl-3a,4,5,6,7,7a hexahydro-7-oxo-1,3a,4-trimethyl-(1*H*)-isoindole (**4c**) and 1-ethoxycarbonyl-6-oxo-3a,4,5,6,6a-pentahydro-1,4,4-trimethyl-(1*H*)-cyclopenta(c)pyrrole (**4d**) in 35,85,24 and 53% yield respectively. Thus reaction of 4, 4-dimethyl-

Table 1.

Diels-Alder reactions of cycloalkenones (1a-d) with 4-methyl-5-ethoxyoxazole(2).[a,b]

Entry No	Dienophile	Product	Reaction condition	Isolatedyields (%)of **4a-d**
1	 **1a**	 **4a**	reflux /48h	35
2	 **1b**	 **4b**	reflux /30min	85
3	 **1c**	 **4c**	sealed tube/ 12h /90°C	24[c]
4	 **1d**	 **4d**	reflux /48h	53[d]

a). All the reactions were carried out in the presence of $ZnBr_2$ in dry benzene.

b). All the compounds were purified on silica gel column chromatography and charactarized by spectral data.[13] c). Nonseparable diastereomers. d). *Cis, trans* (3:1), major *cis* isomeris separable by column chromatography.

-cyclopenta-2-en-1-one (**1d**)[12] was found to be more reactive than dienophile **1a**.

The structure of the products **4a-d** were assigned on the basis of spectral data. The IR spectra of **4a-d** showed absorption at 1740 cm^{-1}corresponding to the ester carbonyl group. Compounds **4a & 4b** showed additional bands at 1690 and 1670 cm^{-1} respectively for the α, β - unsaturated carbonyl group; whereas non-conjugated carbonyl compounds **4c & 4d** displayed absorption at 1710 and 1720 cm^{-1} respectively. ^1H NMR spectra of compounds **4a-d** displayed signals at δ 8.3 (1H, s); 8.4 (1H, s); 7.3 (1H, s) and 7.72 (1H, bs) respectively for C_3-H. ^{13}C NMR spectra of compounds **4a, 4b & 4d** displayed signals at δ 167, 167 and 172 respectively for an ester carbonyl carbon. The compound **4b** structure was confirmed with ^1H COSY and NOE experiments (figure 1.), which indicated long range couplings between C_3-H & C_4-CH_3, C_5-H & C_4-CH_3 and vicinal couplings between C_5-H & C_6-H, methylene and methyl protons of the ethoxy group.

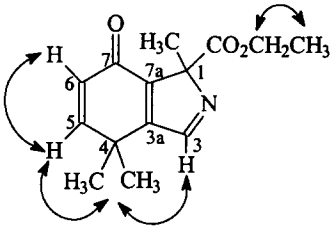


Figure 1.

In conclusion, the present method provides facile route to the synthesis of hydroisoindoles and cyclopenta[c]pyrrole skeletons. In view of the natural occurrence and bioactivities of analogous compounds the present report assumes greater importance.

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13. Compound **4a:** I.R(Film): 1740, 1690, 1630 cm^{-1}. UV(EtOH): λ_{max} 246nm, (ε 7544). ^1H NMR: (300 MHz, $CDCl_3$): δ 8.3 (1H, s), 4.1 (2H, q, J = 7.2 Hz), 2.5 (2H, m), 1.9 (2H, t, J = 7.1Hz), 1.7 (3H, s), 1.35 (3H, s), 1.33 (3H, s), 1.15 (3H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192(s), 167(s), 164(d), 163(s), 152(s), 85(s), 61(t), 38(s), 35(t), 31(t), 26.5(q), 26(q), 19(q), 13(q). Mass: $^m/_z$ 249 (M^+).
Compound **4b:** I.R (Film): 1740, 1670, 1631 cm^{-1}. UV (EtOH): λ_{max} 247nm, (ε 6930). ^1H NMR: (500 MHz, $CDCl_3$): δ 8.4 (1H, s), 6.8 (1H, d, J = 9.9 Hz), 6.2 (1H, d, J = 9.9 Hz), 4.1 (2H, q, J = 7.15 Hz), 1.7 (3H, s), 1.43 (3H, s), 1.4 (3H, s), 1.13 (3H, t, J = 7.15 Hz). ^{13}C NMR: (125 MHz, $CDCl_3$): δ 180(s), 167(s), 164(d), 160(s), 156(d), 153(s), 128(d), 85(s), 62(t), 36(s), 26(q), 25(q), 19(q), 14(q). Mass: $^m/_z$ 247 (M^+).
Compound **4c:** I.R (Film): 1740, 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.3 (1H, s), 7.25 (1H, s), 4.2 (4H, dq, J = 7.2 Hz), 2.7 (1H, s), 2.55 (1H, s), 1.74 (3H, s), 1.72 (3H, s), 1.64 (3H, s), 1.63 (3H, s), 1.38 (3H, d, J = 7.1 Hz), 1.35 (3H, d, J = 7.1 Hz), 2.5-1.45 (10H, m), 1.25 (6H, dt, J = 7.2). Mass: $^m/_z$ 251 (M^+).
Compound **4d (*cis*):** IR (Film): 1740, 1720, 1628 cm^{-1}. ^1H NMR: (300 MHz, $CDCl_3$): δ 7.69 (1H, br, s), 4.2 (2H, q, J = 7.15 Hz), 3.4 (1H, d, J = 7.87 Hz), 2.8 (1H, dd, J = 1.28 and 7.87 Hz), 2.14 (1H, d, J = 16.8 Hz), 2.0 (1H, d, J = 16.8Hz), 1.46 (3H, s), 1.4 (3H, s), 1.3 (3H, t, J = 7.15 Hz), 1.08 (3H, s).
Compound **4d (*trans*):** I.R (Film): 1740, 1720, 1628 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (1H, bs), 4.2 (2H, q, J = 7.15 Hz), 3.45 (1H, d, J = 8.2 Hz), 3.2 (1H, dd, J = 1.83 and 8.2 Hz), 2.14 (1H, d, J = 16.8 Hz), 2.0 (1H, d, J=16.8Hz), 1.52 (3H, s), 1.37 (3H, s), 1.3 (3H, t, J = 7.15 Hz), 1.25 (3H, s).
Compound **4d (*cis* & *trans*):** ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.14, 214.55, 172.39, 171.33, 168.42, 167.18, 83.72, 83.16, 65.56, 64.04, 61.88, 61.58, 58.29, 54.65, 52.96, 52.25, 36.93, 36.76, 30.51, 30.19, 29.70, 25.61, 25.50, 21.02, 14.06, 13.91. Mass: $^m/_z$ 237 (M^+).

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