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Novel regioselective synthesis of decahydrobenzocarbazoles using rhodium generated carbonyl ylides with indoles

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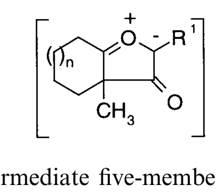
Abstract—Intermolecular cycloadditions of five-membered cyclic carbonyl ylides **3** with indole, *N*-methylindole and *N*-benzylindole afforded decahydrobenzo[*c*]carbazole **4a–f** or decahydrocyclopenta[*c*]carbazole **4g–h** derivatives with high regioselectivity. With *N*-benzoylindole and *N*-sulphonylindole, decahydrobenzo[*c*]carbazoles **4i,j** and the regioisomer decahydrobenzo[*a*]carbazoles **5i,j** are isolated. The electron withdrawing substituent reduces both regioselectivity and reactivity of the cycloadditions. This methodology generated oxa-bridged (unnatural) decahydrobenzocarbazole derivatives with complete control of four stereocenters.

Inter- and intramolecular dipolar cycloadditions have found wide application in the synthesis of a variety of heterocyclic systems, with those of the bimolecular 1,3-dipolar type being the most extensively studied.[1] 1,3-Dipolar cycloaddition offers a versatile route[2] for the construction of a variety of complex five-membered heterocycles that are synthetically useful compounds. The carbonyl ylide 1,3-dipolar cycloaddition reaction has been applied to the synthesis of various natural products such as illudin[3] (sesquiterpene), phorbol esters[4] (diterpene) and brevicomin[5] (pheromone). Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for tetrahydrofuran formation.[6] Five-membered-ring heteroaromatics such as furan, thiophene, and indole have, in spite of their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene.[7] The dipolarophilic reactivity of these heteroaromatic dipolarophiles is however sharply decreased because of the loss of aromaticity in the cycloaddition transition states. The dipolarophilic reactivity[8] of indole derivatives in Diels–Alder reactions with tetrazines[9] and 1,3-dipolar cycloadditions with nitrile imines,[10] azides,[11] ozone,[12] nitrile oxides,[13] isomunchnones[14] has been reported. Surprisingly, the cycloaddition of carbonyl ylides with heteroaromatic compounds has not been studied in the literature. In conjunction with our continuing interest[15] into the synthesis of oxa-polycyclic systems, we describe in this letter, the preliminary results of remarkable intermolecular carbonyl ylide cycloaddition reactions with π-bonds of indole compounds which lead to benzocarbazole derivatives; well known antitumor agents,[16] also used as photoreceptors in electrophotography.[17]

It was envisaged that the reaction of α–diazo carbonyl compounds **1** in the presence of rhodium(II) acetate dimer, can generate five-membered cyclic carbonyl ylides **3** (Fig. 1). To investigate the intramolecular formation and intermolecular 1,3-dipolar cycloaddition reactions of carbonyl ylides **3** with heteroaromatic π-bonds in tandem fashion, α–diazo carbonyl compounds **1** and substituted indoles **2** were assembled from commercially available materials. The α–diazo carbonyl compounds **1a,d,g** were prepared according to our recent work[15] from the corresponding carboethoxy cycloalkanones. The required substituted indoles were obtained according to literature[18] methods.

We investigated the rhodium(II) catalyzed behavior of the above α–diazo carbonyl compounds **1** with substituted indoles **2** in an intermolecular fashion. The reaction of α–diazo carbonyl compound **1a** and indole (**2a**)



3a,d,g
(n = 0,1)

Figure 1. Intermediate five-member-ring carbonyl ylides.

Keywords: diazo compounds; indoles; carbonyl ylides; cycloaddition; rhodium acetate catalyst.

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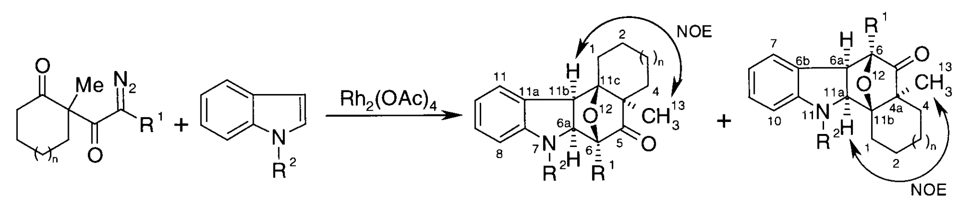

1a,d,g **2** **4** **5**

Scheme 1.

with 0.3 mol% rhodium(II) acetate dimer catalyst in dry dichloromethane was stirred at room temperature under an argon atmosphere for an hour. The chromatographic purification of the above reaction mixture using neutral alumina column furnished the product **4a** in 71% yield (Scheme 1) with high regioselectivity.

The presence of a singlet at δ 4.34, doublets at δ 4.16 and 3.72 for the bridgehead H-6 proton, H-6a and H-11b protons, respectively, in the ^{1}H NMR spectrum of the product; an oxygen attached tertiary bridgehead CH-signal (C-6) at δ 87.7 and a quaternary carbon (C-11c) at δ 90.3 in the ^{13}C NMR spectrum, DEPT and nOe experiments confirmed the formation of the oxa-bridged decahydrobenzo[*c*]carbazole system **4a**.

We subsequently investigated the Rh(II) catalyzed behavior of the α–diazo carbonyl compounds with indoles having an electron donating substituent on the indole nitrogen atom (**2b–c**) which furnished the cycloadducts **4b–c**, respectively in very good yield (Table 1) with complete regioselectivity. We were further interested to study the rhodium(II) catalyzed reactions with a different ring size (*n*) and substituent (R^1) on the diazo substrate **1**. The reaction of α–diazo carbonyl compounds **1d,g** with indole, *N*-methylindole and *N*-benzylindole afforded only decahydrobenzo[*c*]carbazole derivatives **4d–h** in moderate to good yields with high regioselectivity. The presence of an electron withdrawing substituent on the indole nitrogen atom (**2i–j**) afforded a mixture of products[19] **4i–j** and **5i–j** without any regioselectivity.

nOe experiments were performed at 25°C in deutrated chloroform to characterize the regioisomers **4** and **5**. Examination of the nOe experiment on the products **4a–j** explicitly indicated that the protons at C(13) on the methyl function underwent an nOe interaction with the proton located at C(11b). In the other regioisomers **5i** and **5j**, the proton at C(13) on the methyl function and the one at C(11a) characteristically experienced an nOe and the proton at C(11a) of the compound **5j** (Fig. 2) in turn interacted with the aromatic proton located at C(19). The assignment of *exo*-addition was made upon inspection of the ^{1}H NMR spectra; the bridgehead H-6 proton (when R^1 = H) of compounds **4** and **5** showed a singlet without any coupling.

The stereochemical assignments of regioisomers **4a** and **5j** were unambiguously established by X–ray crystallography.[20] Typically the quantity of the catalyst was maintained only at 0.3 mol% for performing the above experiments. In all reactions, the exclusive products in the presence of indoles as dipolarophiles were the *exo*–isomers of oxa–bridged decahydrobenzocarbazoles/decahydrocyclopentacarbazoles. No products resulting from the potential competitive intramolecular C–H insertion[21] and intermolecular N–H insertion[22] reactions (when R^2 = H) of the rhodium carbenoid could be detected. The above results show that the mechanism by which **1a,d,g** were converted into **4** and **5** involves rapid cyclization of the rhodium carbenoid onto the neighboring ring carbonyl group to give the five-membered cyclic carbonyl ylides **3a,d,g,** respectively, as intermediates, followed by [3+2]-cycloaddition with the indole derivatives **2** as dipolarophiles.

In conclusion, we have demonstrated that five-membered cyclic carbonyl ylides **3** generated from the Rh(II) catalyzed reaction of α–diazo carbonyl compounds **1**

Table 1. Yields of oxa-bridged indole derivatives **4** and **5** obtained via scheme

Substrate	*n*	R^1	R^2	Yield[a] % (**4**:**5**)	Mp of **4** (°C)	Mp of **5** (°C)
a	1	H	H	71:0	173–175	–
b	1	H	CH_3	84:0	115–117	–
c	1	H	CH_2Ph	85:0	204–206	–
d[b]	1	COOEt	H	69:0	155–157	–
e[b]	1	COOEt	CH_3	82:0	150–152	–
f[b]	1	COOEt	CH_2Ph	86:0	178–180	–
g	0	H	H	34:0	148–150	–
h	0	H	CH_3	44:0	134–136	–
i	1	H	COPH	22:14	164–166	161–163
j	1	H	SO_2Ph	8:24	160–162	203–205

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds **4** and **5**.

[b] Dry benzene was used as the solvent and the reaction mixture was refluxed.

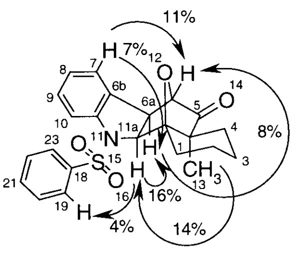

Figure 2. Illustrative nOe results for cycloadduct **5j**.

undergo successful 1,3-dipolar cycloaddition across indole π-bonds to provide novel oxa-bridged decahydrobenzocarbazoles/decahydrocyclopentacarbazoles in a facile manner. The presence of an electron withdrawing substituent on the indole nitrogen atom provided lower reactivity towards the carbonyl ylide cycloaddition and loss of regioselectivity was observed. This tandem intramolecular cyclization-intermolecular cycloaddition sequence is particularly attractive as four stereocenters and two carbon–carbon bonds are formed in a single step with a high degree of stereocontrol under mild experimental conditions. Further studies on the reactivity of heteroaromatic compounds towards carbonyl ylides are in progress.

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19. All new compounds exhibited spectral data consistent with their structures. Selected spectral data, 7-Benzenesulfonyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1H-benzo[*c*]carbazole (**4j**): mp 160–162°C; IR (KBr) 2925, 2854, 1761 (C=O), 1638, 1459, 1361, 1263, 1168, 1090, 1033, 755 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (s, 3H, CH_3), 1.22–2.13 (m, 8H), 3.57 (d, 1H, $J=8.1$ Hz, H-11b), 4.32 (d, 1H, $J=8.1$ Hz, H-6a), 4.93 (s, 1H, H-6), 6.97–7.01 (m, 2H), 7.25–7.28 (m, 1H), 7.43–7.55 (m, 3H), 7.66–7.81 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.2 (CH_3), 20.2 (CH_2), 22.0 (CH_2), 25.5 (CH_2), 30.4 (CH_2), 49.5 (C-11b), 50.8 (C-4a), 67.5 (C-6a), 87.0 (C-6), 91.9 (C-11c), 114.3 (Arom-CH), 123.1 (Arom-CH), 126.6 (*quat-C*), 127.2 (Arom-CH), 127.4 (Arom-CH), 128.8 (Arom-CH), 129.0 (Arom-CH), 129.2 (*quat-C*), 133.4 (Arom-CH), 154.3 (*quat-C*), 212.8 (C-5); EIMS *m*/*z* 409 (M^+); Anal. Calcd for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42. Found: C, 67.58; H, 5.71; N, 3.39. 11-Benzenesulfonyl-6,11b-epoxy-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-4a-methyl-5-oxo-1H-benzo[a]carbazole (**5j**): mp 203-205°C; IR (KBr) 2928, 1758 (C=O), 1640, 1600, 1452, 1359, 1263, 1168, 1088, 1031, 757 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (s, 3H, CH_3), 1.26–1.88 (m, 6H), 1.98–2.15 (m, 1H), 2.35–2.44 (m, 1H), 3.42 (d, 1H, $J=7.7$ Hz, H-6a), 4.30 (s, 1H, H-6), 4.44 (d, 1H, $J=7.7$ Hz, H-11a), 7.05-7.10 (m, 1H), 7.26–7.39 (m, 4H), 7.47–7.56 (m, 3H), 7.70 (d, 1H, $J=8.2$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.8 (CH_3), 20.4 (CH_2), 21.8 (CH_2), 24.4 (CH_2), 29.7 (CH_2), 48.7 (C-6a), 49.2 (C-4a), 67.2 (C-11a), 84.8 (C-6), 91.4 (C-11b), 117.2 (Arom-CH), 124.5 (Arom-CH), 125.6 (Arom-CH), 127.2 (Arom-CH), 129.0 (Arom-CH), 130.8 (*quat-C*), 133.4 (Arom-CH), 136.5 (*quat-C*), 156.1 (*quat-*

C), 215.6 (C-5); EIMS *m*/*z* 409 (M^+); Anal. Calcd. for $C_{23}H_{23}NO_4S$: C 67.46, H 5.67, N 3.42; found: C 67.34, H 5.62, N 3.45%.

20. The X-ray crystal structure analyses will be reported elsewhere.
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