A Novel Cycloaddition Reaction for Obtaining Polycyclic 2,2,3,3-Tetrasubstituted-1*H*-indoles

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Fused heteroaromatic systems, such as indoles and indazoles bearing functional groups such as hydroxyl at specific positions, are among the most basic and attractive targets of organic synthesis.[1]

We have already proposed a novel cycloaddition process for obtaining various 1*H*-indol-5-ols from 3-alkenyl-4-(arylazo)phenols in previous papers.[2] These reactions proceed in good yields at unusually mild reaction conditions and in a short reaction time.

There has been a great deal of interest in the chemistry of various 1*H*-indoles because of their biological and industrial applications, and very few polycyclic 1-unsubstituted-alkyl- and/or -alkoxy-2,2,3,3-tetrasubstituted-1*H*-indole derivatives have been synthesized.[3]

Here, we describe a novel cycloaddition reaction using tetrahydrocyclopenta[*b*]indoles for obtaining polycyclic 2,2,3,3-tetrasubstituted-1*H*-indoles.

The reactions of three types of 2,3-cycloalkano[*b*]-indoles with a 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone in the presence of sulfuric acid were investigated. The starting 2,3-cycloalkano[*b*]indoles are (type-1) 5-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indole, which has a five-membered ring moiety capable of taking the indolenine type structure, (type-2) 1-ethyl-5-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indole, which has a strained five-membered ring moiety capable of taking the indolenine type structure, and (type-3) 6-methoxy-1,2,4,6-tetrahydrocarbazole, which has a stable six-membered ring.

In the case of type-1, a novel cycloaddition reaction giving polycyclic 2,2,3,3-tetrasubstituted-1*H*-indoles was found.[4]

We report the details below and discuss a plausible reaction scheme of this new cycloaddition reaction (Scheme 1).

Type-2 and type-3 indoles gave only one reaction product of the indole with 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone (1:1 reaction ratio with xanthene compound, hereafter cited as compounds S-2 and S-3, respectively).

Type-1 indole gave three products, compound S-1 (1:1 reaction ratio) and two products (1:2 reaction ratio) of indole with 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone (hereafter cited as compounds A and B).

Compound S-1 is a minor product while compounds A and B are major products, which are stereoisomers having very similar IR spectra and the same chemical formula.[5]

Results are summarized in Table 1.

In the step-2 process to produce cyclized products A and B, the initial electrophilic attack of benzophenone at the position 3 of the indole must produce an indolenium cation, which in the case of NH-indole (type-1) may exist in equilibrium with the conjugate base, the indolenine.[6]

The indolenium cation can then cyclize by nucleophilic addition of the hydroxyl of the 3-hydroxybenzyl substituent to the indolenine double bond, giving a spiro-cyclized compound, decreasing the ring strain of the cyclopentene to cyclopentane.

According to the addition of the hydroxyl to the indolenine double bond from different faces of the type-1 indole, two stereoisomers are possible.

The stereochemistry of A and B is not clarified yet (see Scheme 1, cyclopentane ring and intermediate).

In the case of type-2, a cyclized product, *N*-ethyl-2,2,3,3-tetrasubstituted-1*H*-indole, wherein the intermediate ethyl iminium cation from type-2 indole is thought to be as stable as an indolenium cation from type-1 indole, was not produced under these reaction conditions.

We suggest two factors which prevent cyclization of the type-2 indole: (a) a steric effect by the ethyl group to the addition of a hydroxyl group to the iminium double bond and (b) unstability of the cyclized compound by the large steric hindrance of the *N*-ethyl substituent at position 1 with 2,2-substituents, canceling the stabilizing effect of ring strain from cyclopentene to cyclopentane.

Thus the stability of the ethyl iminium cation from type-2 indole, under the reaction conditions, allows the intermediate to revert to starting materials.

S-3 from a type-3 indole is thought to be stable under these reaction conditions and a step-2 reaction was not observed.[7]

Type-1 indole provides a useful route for obtaining various kinds of polycyclic 2,2,3,3-tetrasubstituted-1*H*-indoles, suggesting the importance of the presence of a

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(2) Satomura, M. *J. Org. Chem.* **1993**, *58*, 3757, 6936.

(3) 2,2,3,3-Alkyl- or -alkoxy-substituted-1*H*-indoles, see: (a) Gallagher, T.; Magnus, M. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (b) Le Menez, P.; Sapi, J.; Kunesch, N.; Angell, E. C.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 3216. (c) Ciganek, E. *Ibid.* **1992**, *57*, 4521. (d) Barnwell, N.; Beddoes, R. L.; Mitchell, M. B.; Joule, J. A. *Heterocycles* **1994**, *37*, 175. (e) Brown, D. W.; Graupner, P. R.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1991**, *47*, 4383. (f) WO patent, 90/15779, 92/6956; *Chem. Abstr.* **1992**, *117*, 48334y. Cyclic 2,2,3,3-tetrasubstituted-1*H*-indoles are derived from tetrahydroindeno[1,2-*b*]indole through alkylation with alkyllithium.

(4) On cycloaddition reactions, see: (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (c) Comprehensive *Organic Chemistry*; Trost, B. M., Freming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5. (d) Ellis, G. P. *Synthesis of Fused Heterocycles*; John Wiley & Sons: New York; Part 1, 1987; Part 2, 1992.

(5) Compounds **A**, **B**, **S**, and derivatives thereof are disclosed in our patent, Fuji Photo Film Co. Ltd., Tokkai-Hei 5-59060, Satomura, M.; Takeda, A.; Katoh, H. (*Chem. Abstr.* **1993**, *119*, *117229y*). Compounds A and B are useful color formers for the thermosensitive papers having black color hue when used in combination with an acidic component. Details of color formers and thermosensitive systems are disclosed in Satomura, M. *Organic Materials For Imaging*; Edited by The Japanese Research Association for Organic Electronics. Bunshin Publishing Co.: Tokyo, 1993; Chapter 4.

(6) On reaction of phenol to azomethine group, see: Miyano, S.; Abe, N. *Tetrahedron Lett.* **1970**, *22*, 1909.

(7) For xanthene type color formers having the indole moiety (S-1–S-3), see: Fuji Photo Film Co. Ltd., Jpn. Tokkai-Hei 4-187688, Satomura, M.; Takeda, A. (*Chem. Abstr.* **1992**, *117*, 214541k). For xanthene type color formers having the indolenine moiety, see: Fuji Photo Film Co. Ltd., Jpn. Tokkai-Hei 4-187687, Satomura, M.; Takeda, A. (*Chem. Abstr.* **1992**, *117*, 214540j).

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Scheme 1. Synthesis of Polycyclic Tetrasubstituted-1*H*-indole

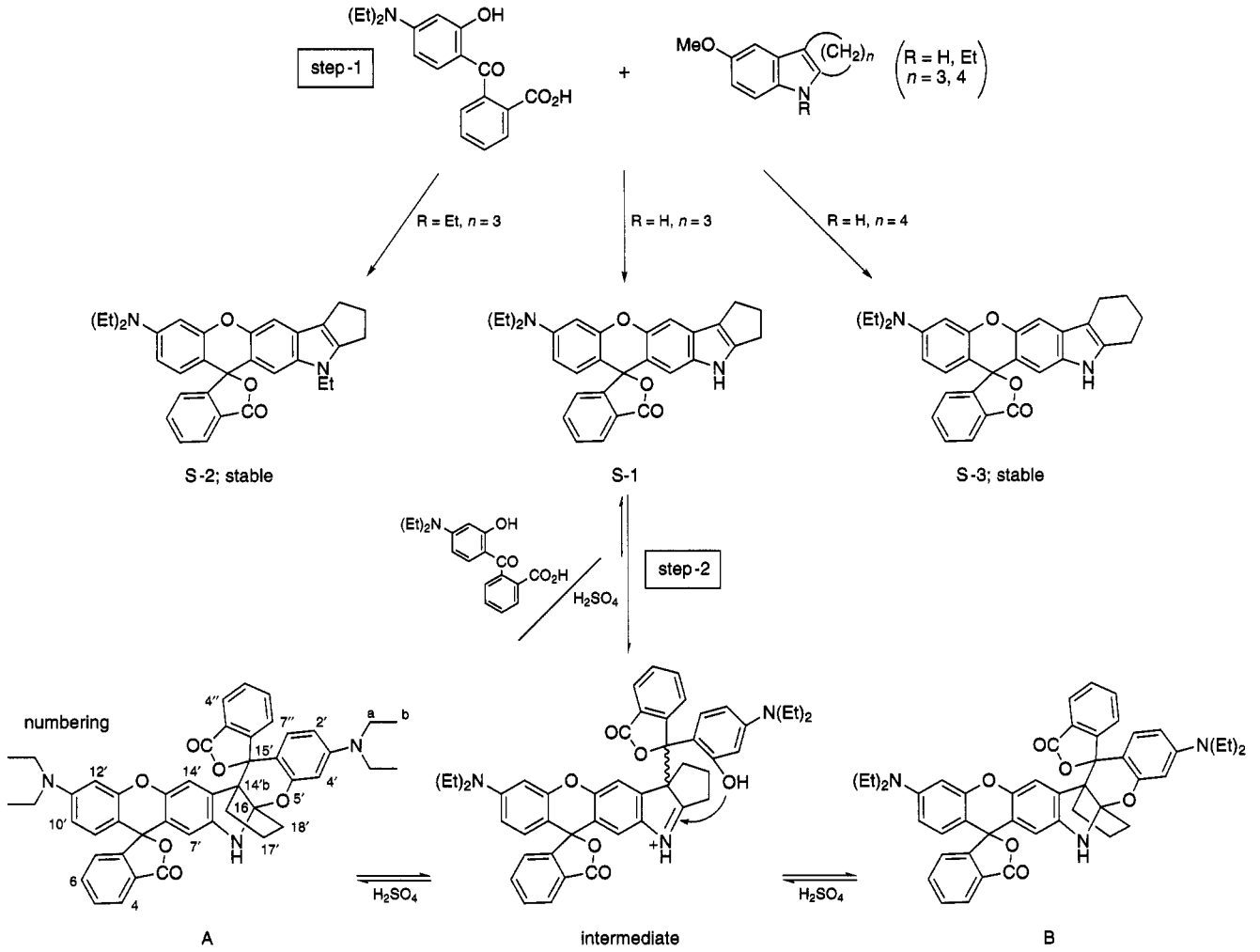

Table 1. Synthesis of Polycyclic 2,2,3,3-Tetrasubstituted-1*H*-indoles

				S			A		B	
type	ring size	R[a]	run[b]		yield, %	mp, °C	yield, %	mp, °C	yield, %	mp, °C
1	5	H	1	S-1	5	285–261	20	273–274	20	293–294
			2	S-1	10		40		40	
2	5	Et		S-2	90	235				
3	6	H		S-3	90	305				

[a] R = substituent at position 1. [b] Run-2, 2 molar equiv of 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone to 1 for the indole compound are used.

hydrogen atom at position 1 and a cyclopenta[*b*]indole ring moiety for the cycloaddition reaction.

It is of merit of this cycloaddition reaction that, in one step, a complicated, highly functionalized system can be assembled from a simple indole. As described above, under very mild reaction conditions 2,2,3,3-tetrasubstituted-1*H*-indoles A and B are readily prepared from cyclopenta[*b*]indole or S-1 in excellent yield at approximately a 1:1 ratio. Further, when isolated A or B is treated with sulfuric acid, a mixture of A and B (at approximately a 1:1 ratio) and S-1 is found, showing acid-catalyzed mutual conversion of stereoisomers.

When isolated S-1 is treated with an equimolar amount of 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone in sulfuric acid at room temperature for about 30 min under stirring, A and B (at approximately a 1:1 ratio) are produced.

The 1-ethyl derivative (type-2) and tetrahydrocarbazole derivative (type-3) under the same reaction conditions gave no appreciable amount of polysubstituted-1*H*-indole products, as described above.

Thus, 1,2,3,4-tetrahydrocyclopenta[*b*]indoles having a substituent, that is, having no hydrogen atom at position 1, do not give 2,2,3,3-tetrasubstituted-1*H*-indoles according to this novel cyclization reaction. These results support the above-proposed reaction scheme and the presence of indolenium cation type intermediate.

When compared with the previous 2,2-substituted-1*H*-indole process, this process offers several advantages. First, a polycyclic 2,2,3,3-tetrasubstituted-1*H*-indole is obtained conveniently. Second, it is obtained directly from 1,2,3,4-tetrahydrocyclopenta[*b*]indoles. Third, the reaction conditions adopted in this process are all extraordinarily mild. All the steps can be conducted at temperatures below 30 °C. Fourth, the starting raw materials for our process are, in general, readily available and inexpensive.[3] Finally, the reaction is completed in

a short reaction time. The yields are superior or comparable to the average yields of the current processes.

We will apply this novel cycloaddition reaction to the preparation of various complicated polycyclic 2,2,3,3-tetrasubstituted-1*H*-indoles to improve their current synthesis.

Conclusion

A reaction of 1,2,3,4-tetrahydrocyclopenta[*b*]indole which has no substituent at position 1 with 2′-carboxy-2-hydroxybenzophenone provides a useful route to obtain various kinds of polycyclic 2,2,3,3-tetrasubstituted-1*H*-indoles.

The mild reaction conditions under which synthesis of our 1*H*-indoles proceeds should permit the construction of this ring system even in the presence of functional groups which are sensitive to elevated temperature, strong bases, reduction, or oxidation.

Research is in progress to further define the scope and limitations of this novel cyclization reaction.

Experimental Section

Unless otherwise indicated, materials were obtained from commercial suppliers and used without further purification. General purification procedures are the same as those reported.[2] Melting points are uncorrected. NMR spectra were recorded on a Varian Unity-400 spectrometer, equipped with a Cryomagnet Systems ^{1}H probe with a decoupling coil for irradiation of ^{13}C, as a solution in $CDCl_3$ for compound A. The internal standard is TMS. HRMS (FAB$^+$) were observed with a JEOL-SX102A.

General Procedure. To a flask containing an ice-cooled mixture of sulfuric acid (8 mL) and fuming sulfuric acid (2 mL) were added methoxy-2,3-cycloalkano[*b*]indole (0.01 mol) and 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone (0.01 mol) (in the case of run 2, 0.02 mol) slowly, and the solution was stirred for 2 h at room temperature and for 30 min at 30 °C. The reaction mixture was poured into ice-cooled alkaline water to separate the reaction products. The precipitates were extracted with EtOAc and dried over sodium sulfate. The mixture (S and isomers A and B) was separated by chromatography (silica gel, Merck, silica gel-60) eluted with EtOAc/hexane (volume ratio 2:1). Yields and melting points are shown in Table 1.

Synthesis of A and B from S-1. To a flask containing an ice-cooled mixture of sulfuric acid (8 mL) and fuming sulfuric acid (2 mL) were added compound S-1 (from type-1) (0.01 mol) and 2′-carboxy-4-(diethylamino)-2-hydroxybenzophenone (0.01 mol) slowly, and the solution was stirred for 2 h at room temperature and for 30 min at 30 °C. The reaction mixture was treated as described above and gave compounds A and B (at approximately a 1:1 ratio).

Isomerization of Compounds A or B. To a flask containing an ice-cooled mixture of sulfuric acid (8 mL) and fuming sulfuric acid (2 mL) was added compound A (or B) (0.01 mol) slowly, and the solution was stirred for 2 h at room temperature and for 30 min at 30 °C. Then, the reaction mixture was treated as described above and gave compounds A and B (at approximately a 1:1 ratio) and S-1.

Compound A, 3′,11′-Bis(diethylamino)dispiro[isobenzofuran-1,8′-(5′a,14′b-propano[1]benzopyrano[2,3-*b*]-[1]benzopyrano[2,3-*f*]indole-15′,1″-isobenzofuran)]-3,3″-dione. Calcd for $C_{47}H_{43}N_3O_6$: C, 75.68; H, 5.81; N, 5.63. Found: C, 75.64; H, 5.88; N, 5.55. ^{1}H NMR δ ppm ($CDCl_3$): 7.92 (4), 7.52 (5), 7.59 (6), 7.12 (7), 6.83 (1′), 6.12 (2′), 6.30 (4′), 4.26 (6′), 7.10 (7′), 6.51 (9′), 6.28 (10′), 6.39 (12′), 5.72 (14′), 2.40 (18′), 1.50 (17′), 1.80 (16′), 7.95 (4″), 7.53 (5″), 7.64 (6″), 7.85 (7″), 3.35 (a or a′), 1.30 (b or b′), 3.25 (a′ or a), 1.10 (b′ or b). ^{13}C NMR δ ppm: 84.8 (1), 126.7 (3a), 125.8 (4), 129.1 (5), 134.6 (6), 124.1 (7), 151.7 (7a), 124.5 (1′), 106.2 (2′), 149.3 (3′), 102.3 (4′), 153.6 (4′a), 107.3 (5′a), 145.5 (6′a), 104.0 (7′), 118.3 (7′a), 104.6 (8′a), 128.6 (9′), 108.0 (10′), 149.4 (11′), 97.7 (12′), 152.9 (12′a), 145.0 (13′a), 115.8 (14′), 134.1 (14′a), 66.2 (14′b), 89.3 (15′), 113.7 (15′a), 41.9 (18′), 23.0 (17′), 37.4 (16′), 126.1 (3″a), 124.7 (4″), 129.3 (5″), 134.4 (6″), 124.2 (7″), 154.0 (7″a), 44.6 (a or a′), 12.7 (b or b′), 44.5 (a′ or a), 12.8 (b′ or b). ^{1}H-Detected heteronuclear multiple-bond correlation (HMBC) was performed with a Varian Unity-400 FT-NMR, to determine the ring structure of A.[2]

The observed long-range couplings (^{1}H and ^{13}C) of (7′-^{1}H and 1-^{13}C), (9′-^{1}H and 1-^{13}C), (7-^{1}H and 1-^{13}C), (7″-^{1}H and 15′-^{13}C), (1′-^{1}H and 15′-^{13}C), (16′-^{1}H and 15′-^{13}C), (6′-^{1}H and 14′a-^{13}C), (6′-^{1}H and 6′a-^{13}C), (6′-^{1}H and 5′a-^{13}C), (6′-^{1}H and 14′b-^{13}C), (14′-^{1}H and 14′b-^{13}C), and (16′-^{1}H and 14′a-^{13}C) indicate the proposed structure.

Compound B: stereoisomer of compound A. Calcd for $C_{47}H_{43}N_3O_6$: C, 75.68; H, 5.81; N, 5.63. Found: C, 75.70; H, 5.73; N, 5.56. ^{1}H NMR δ ppm (DMSO-d_6/$CDCl_3$): 7.95–8.0 (m, 4H), 7.78–7.86 (m, 2H), 7.72 (t, 1H, J = 7.2 Hz), 7.25 (d, 1H, J = 7.5 Hz), 6.87 (s, 1H), 6.6 (d, 1H, J = 8.6 Hz), 6.40–6.44 (m, 2H), 6.32 (d, 1H, J = 1.9 Hz), 6.29 (dd, 1H, J = 2.4 Hz), 6.2 (dd, 1H, J = 2.4, 8.7 Hz), 5.7 (s, 1H), 5.6 (s, 1H). ^{13}C NMR δ ppm: 168.6, 168.3, 154.4, 152.27, 152.23, 149.6, 149.1, 147.1, 146.4, 143.1, 135.5, 134.5, 133.1, 130.4, 130.0, 128.5, 127.5, 126.3, 126.2, 125.2, 124.9, 124.4, 124.0, 118.2, 111.7, 111.5, 108.2, 106.7, 105.0, 103.6, 102.7, 101.5, 96.6, 87.8, 65.2, 43.6, 21.9, 12.2.

Compound S-1. 9-(Diethylamino)-1,2,3,4-tetrahydrospiro-[6*H*-[1]benzopyrano[2,3-*f*]cyclopenta[*b*]indole-6,1′(3′*H*)-isobenzofuran]-3′-one. HRMS, FAB$^+$. Calcd for $C_{29}H_{27}N_2O_3$ (M + H)$^+$: 451.2022. Found: 451.2061.

Compound S-2. 9-(Diethylamino)-4-ethyl-1,2,3,4-tetrahydrospiro[6*H*-[1]benzopyrano[2,3-*f*]cyclopenta[*b*]indole-6,1′(3′*H*)-isobenzofuran]-3′-one. Calcd for $C_{31}H_{30}N_2O_3$: C, 77.79; H, 6.32; N, 5.85. Found: C, 77.41; H, 6.41; N, 5.72. ^{1}H NMR δ ppm (DMSO-d_6/$CDCl_3$): 7.9 (d, 1H, J = 8.0 Hz), 7.72 (m, 1H, J = 1.2, 7.4 Hz), 7.66 (m, 1H, J = 1.0, 7.4 Hz), 7.20 (d, 1H, J = 7.2 Hz), 7.17 (s, 1H), 6.50 (s, 1H), 6.47 (d, 1H, J = 9.0 Hz), 6.42 (d, 1H, J = 2.3 Hz), 6.30 (dd, 1H, J = 9.0 Hz).

Compound S-3. 3-(Diethylamino)-8,9,10,11-tetrahydrospiro[[1]benzopyrano[3,2-*b*]carbazole-13(7*H*),1′(3′*H*)-isobenzofuran]-3′-one. HRMS, FAB$^+$. Calcd for $C_{30}H_{29}N_2O_3$ (M + H)$^+$: 465.2141. Found: 465.2210. ^{1}H NMR δ ppm (DMSO-d_6); 8.0 (d, 1H, J = 7.5 Hz), 7.8 (m, 1H, J = 1.2, 7.5 Hz), 7.7 (m, 1H, J = 1.0, 7.4 Hz), 7.3 (d, 1H, J = 7.5 Hz), 7.2 (s, 1H), 6.53 (s, 1H), 6.50 (d, 1H, J = 8.8 Hz), 6.45 (d, 1H, J = 2.3 Hz), 6.40 (dd, 1H, J = 2.5, 8.9 Hz).

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