JOC*Note*

Indium-Mediated 1,2,4,5-Hexatetraen-3-ylation of 4-Acetoxy-2-azetidinones and Their Applications to the Diels−Alder Reactions for the Synthesis of 2-Azetidinone Derivatives

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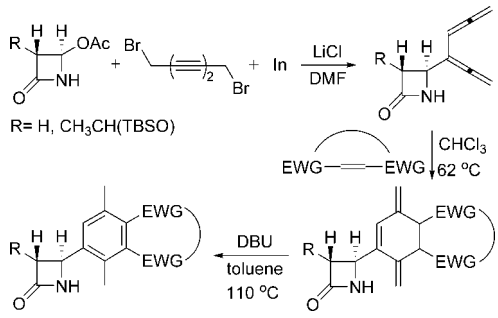

4-Acetoxy-2-azetidinones reacted with organoindium reagent generated in situ from indium and 1,6-dibromo-2,4-hexadiyne in the presence of LiCl in DMF to selectively produce 2-azetidinones possessing 1,2,4,5-hexatetraen-3-yl group on the C4-position. The Diels−Alder reactions of 4-(1,2,4,5-hexatetraen-3-yl)-2-azetidinones with a variety of dienophiles and subsequent aromatizations afforded valuable functional group-substituted 2-azetidinones in good yields.

Because the 2-azetidinone nucleus is the central building blocks of β-lactam antibiotics, functionalization of the 2-azetidinone framework is essential for the development of new β-lactam antibiotics.[1] Therefore, introduction and transformation of functional groups on the ring of 2-azetidinones is one of the most important motifs in β-lactam chemistry.[2] Although introduction of various heteroatoms such as oxygen, halide, and nitrogen on the C4-position of 2-azetidinone have been reported, the selective introduction of carbon nucleophiles, such as vinyl,[3] ethynyl,[4] allyl,[3] propargyl,[5] allenyl,[6] 1,3-butadien-1-yl,[7] and 1,3-butadien-2-yl[8] groups, is mostly attractive and fundamental problem in the synthesis of β-lactam antibiotics due to further functionalization of these groups.[9] In general, it has been accomplished by the ability of 4-acetoxy-2-azetidinone to take part in to nucleophilic substitution reactions very easily on the C4-position, these taking place via acyliminium intermediates.[10] Therefore, lots of efforts have been devoted to the selective introduction of these groups via the reaction of 4-acetoxy-2-azetidinones with a variety of organometallic compounds.[1b] In the context of our ongoing research interest in synthesis of functionalized β-lactam compounds using a variety of generated in situ organoindium reagents,[11] we reported selective indium-mediated propargylation, allenylation, and 1,3-butadien-2-ylation reactions and their applications to cyclization reactions.[12] However, introduction of 1,2,4,5-hexatetraen-3-yl group on 2-azetidinone ring have been remained a formidable challenge despite the enormous further functionalization through the Diels−Alder reactions as well as aromatizations of adducts and transition metal-catalyzed cyclizations of 1,2,4,5-hexatetraen-3-yl group.[13] Described herein is the selective introduction of 1,2,4,5-hexatetraen-3-yl group on C4-position of 2-azetidinones with organoindium reagent generated in situ from indium and 1,6-dibromo-2,4-hexadiyne and subsequent the Diels−Alder reactions and aromatizations for the synthesis of 2-azetidinone derivatives (Scheme 1).

At the outset, optimum conditions for indium-mediated 1,2,4,5-hexatetraen-3-ylation on C-4 position of 2-azetidinones

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SCHEME 1. 1,2,4,5-Hexatetraen-3-ylations and Aromatizations

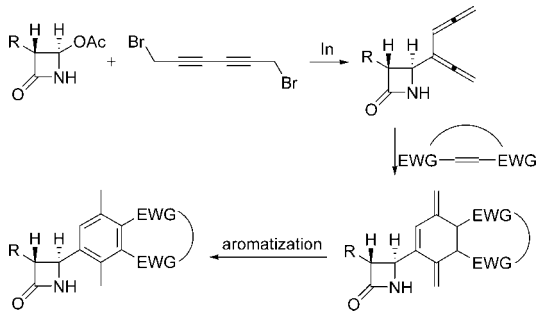
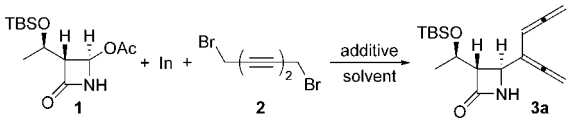


TABLE 1. Optimization of 1,2,4,5-Hexatetraen-3-ylation



entry	In (equiv)	2 (equiv)	additive (equiv)	solvent	temp (°C)	time (h)	yield (%)[a]
1	2.2	1.1	LiCl (2.2)	DMF	25	3	36
2	2.2	1.1	LiBr (2.2)	DMF	25	2.5	46
3	2.2	1.1	LiI (2.2)	DMF	25	18	0
4	2.2	1.1	−	DMF/H_2O[b]	70	5	5 (28)[c]
5	2.2	1.1	LiCl (2.2)	DMF/H_2O[b]	70	12	0
6	2.2	1.1	LiI (2.2)	DMF/H_2O[b]	70	12	0
7	3.0	2.5	LiCl (3.0)	THF	25	24	0
8	3.0	2.5	−	DMF	25	3	38
9	3.0	2.5	LiCl (3.0)	DMF	25	3	63
10	3.0	2.5	LiBr (3.0)	DMF	25	4	40
11	3.0	2.5	LiI (3.0)	DMF	25	3	37

[a] Isolated yield. [b] DMF/H_2O = 2:1. [c] 1,3,5-Hexatetraen-3-yl-tethered 2-azetidinone.

were examined by the reaction of 2-azetidinone (**1**) with organoindium reagents generated in situ from indium and 1,6-dibromo-2,4-hexadiyne (**2**) (Table 1). Reactions of **1** with indium (2.2 equiv) and **2** (1.1 equiv) in the presence of LiCl and LiBr (2.2 equiv) in DMF selectively produced the desired product **3a** in 36 and 46% yields, respectively, (entries 1 and 2), whereas LiI gave messy results (entry 3). DMF-H_2O (2:1) as a solvent afforded 1,3,5-hexatetraen-3-yl-tethered 2-azetidinone in 28% yield without additive (entry 4). However, cosolvent of DMF and H_2O gave rise to the messy results in the presence of LiCl and LiI (entries 5 and 6) because bis(allene) **3a** was apt to decompose under these reaction conditions. DMF was the best solvent among several reaction media (DMF, THF, and DMF-H_2O) that were screened. Among several reaction conditions that were examined, the best results were obtained with the organoindium reagent generated in situ from the reaction of indium (3 equiv) with **2** (2.5 equiv) in the presence of LiCl (3 equiv), producing selectively **3a** in 63% yield (entry 9). Surprisingly, there are no diyne compounds (**3b**) through 2,4-hexadiyn-1-ylation, allenynes (**3c** and **3d**) through 4,5-hexadien-2-yn-1-ylation and 1,2-hexadien-4-yn-3-ylation, and 1,6-eliminated compound of **2** (Figure 1).[14] The ^1H and ^{13}C NMR spectra of **3a** are consistent with 2-azetidinone possessing 1,2-bis(allenyl) group. The two *sp* resonances (400 MHz) of 1,2,4,5-hexatetraen-3-yl group appeared at 209.1 and 208.2 ppm. The four sp^2 resonances (400 MHz) of 1,2,4,5-hexatetraen-3-yl group

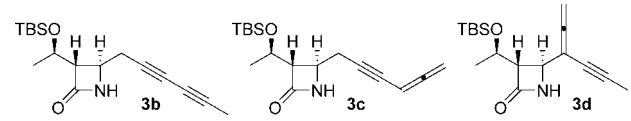
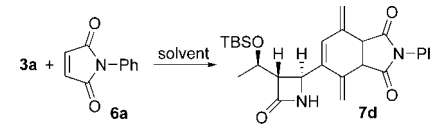


FIGURE 1. Possible products from the reaction of **3a** with indium and **2**.

TABLE 2. Optimization of the Diels−Alder Reactions of 3a with *N*-Phenylmaleimide[a]



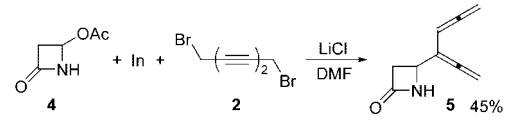
entry	solvent	temp (°C)	time (h)	yield (%)[b]
1	Toluene	110	5	0
2	1,4-Dioxane	25	3	25
3[c]	1,4-Dioxane	25	2	0
4	CH_3CN	25	3	0
5	Benzene	25	2	15
6	CH_2Cl_2	25	1.5	20
7[d]	CH_2Cl_2	25	1.5	20
8[e]	1,4-Dioxane	25	3	18
9[e]	CH_2Cl_2	25	3	20
10[f]	$CHCl_3$	25	24	45
11[g]	$CHCl_3$	25	5	53
12[h]	$CHCl_3$	25	10	70
13[h]	$CHCl_3$	62	4	70 (1:1.6)[i]

[a] Dienophile (4 equiv) was used. [b] Isolated yield. [c] $InCl_3$ (5 mol%) was used. [d] [bmim]SbF_6 (1 equiv) was used. [e] Diene (2 equiv) and dienophile (1 equiv) were used. [f] Diene (1 equiv) and dienophile (1 equiv) were used. [g] Diene (1 equiv) and dienophile (2 equiv) were used. [h] Diene (1.5 equiv) and dienophile (1 equiv) were used. [i] Isomeric ratio.

were seen at 101.0, 90.0, 80.0, and 79.5 ppm, indicating that compound **3a** was selectively produced.

Among the additives examined, LiCl provided the best results under the optimum conditions (entries 9−11). The use of indium in less than 3 equiv and 1,6-dibromo-2,4-hexadiyne (**2**) in less than 2.5 equiv resulted in sluggish reaction and gave lower yields, indicating that the stoichiometry of indium and **2** is critically important for successful reactions. The present method indicates that 1,6-dibromo-2,4-hexadiyne acts selectively as synthon of 3-anion of 1,2,4,5-hexadiyne. These results contrast that 1,6-dibromo-2,4-hexadiyne acts selectively as synthon of 3,6-dianion of 1,2-hexadien-4-yne in the reaction of aldehydes and ketones with organoindium generated in situ from indium and 1,6-dibromo-2,4-hexadiyne.[15]

Encouraged by these results, we examined the reaction of 4-acetoxy-2-azetidinone (**4**) with organoindium reagent, affording 4-(1,2,4,5-hexatetraen-3-yl)-2-azetidinone (**5**) in 45% yield (eq 1).



(1)

Diels−Alder reactions of **3a** with *N*-phenylmaleimide (**6a**) were studied to show the synthetic applicability of 4-(1,2,4,5-hexatetraen-3-yl)-2-azetidinones (Table 2). Treatment of **3a** with **6a** (4 equiv) gave the desired adduct **7d** in 25% yield in 1,4-

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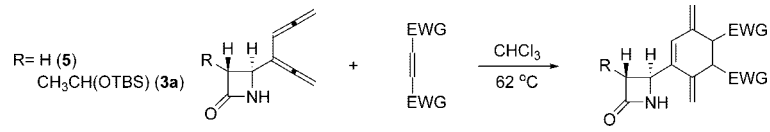
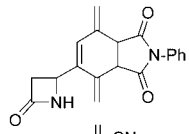
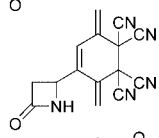
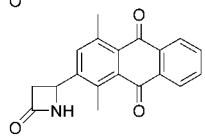
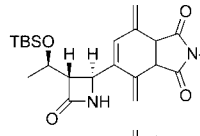
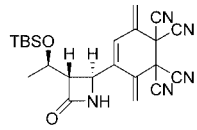
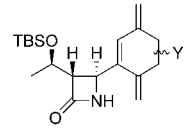
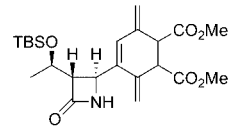
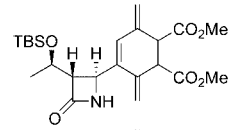
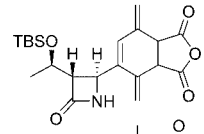
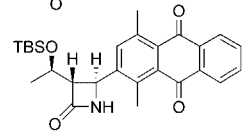
TABLE 3. Diels−Alder Reactions of 1,2,4,5-Hexatetraen-3-yl-tethered 2-Azetidinones with Dienophiles

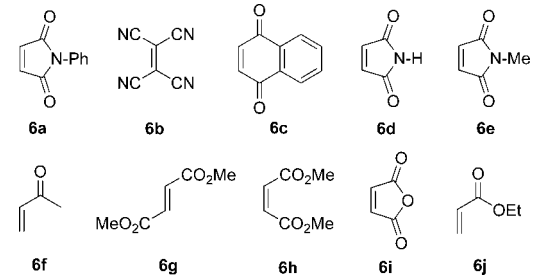


entry	reactants	time (h)	adducts	yeld (%)[a]
1[b]	**5/6a**	4		**7a** 70(1:1)[c]
2[b]	**5/6b**	2		**7b** 75
3[b]	**5/6c**	15		**7c** 65
4[b]	**3a/6a**	4		**7d** 70(1:1.6)[c]
5[b]	**3a/6d**	4		**7e** 65(1:2.3)[c]
6[b]	**3a/6e**	5		**7f** 72(1:2.2)[c]
7[d]	**3a/6b**	2		**7g** 83
8[d]	**3a/6f**	7		**7h** 80(3.3:2:1)[c]
9[d]	**3a/6j**	8		**7i** 65(2:1.8:1)[c]
10[e]	**3a/6g**	18		**7j** 75(1:1.7)[c]
11[b]	**3a/6h**	24		**7k** 49(1:3.7)[c]
12[d]	**3a/6i**	3		**7l** 70(1:1.8)[c]
13[b]	**3a/6c**	15		**7m** 85

[a] Isolated yield. [b] Diene (1.5 equiv) and dienophiles (1 equiv) were used. [c] Isomeric ratio. [d] Diene (1 equiv) and dienophiles (2 equiv) were used. [e] Diene (1 equiv) and dimethyl fumarate (5 equiv) were used.

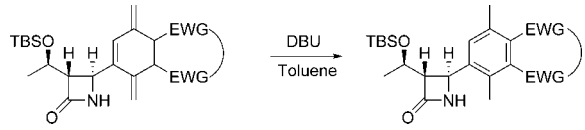
dioxane at 25 °C for 3 h (entry 2). Use of $InCl_3$ (5 mol%) did not produce the desired product (entry 3). Adduct **7d** was only obtained in 20% yield with ionic liquid (1 equiv) as an additive (entry 7). Although a variety of solvents, such as toluene, 1,4-dioxane, acetonitrile, benzene, and dichloromethane, were examined, **7d** was not obtained in good yields (entries 1−7). Because bis(allene) **3a** as well as triene **7d** were easily apt to decompose under the reaction conditions, more than 1 equiv of **3a** was used in some cases. Among several reaction conditions that were examined, the best results were obtained with the reaction of **3a** (1.5 equiv) with **6a** (1 equiv) in $CHCl_3$ at 62 °C for 4 h, producing **7d** in 70% (dr = 1:1.6) yield (entry 13).

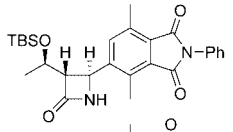
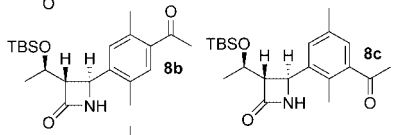
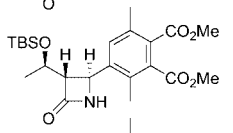
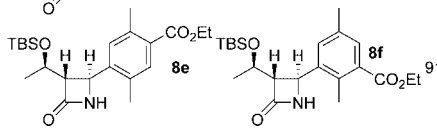
Next, we turned our attention to the Diels−Alder reaction of **3a** and **5** with various dienophiles and the results are summarized in Table 3. Reactions of **5** with dienophiles **6a** and **6b** afforded adducts **7a** and **7b** in 70% (dr = 1:1) and 75% yields, respectively, under the optimum conditions (entries 1 and 2). As shown in entry 3 and 13, the Diels−Alder reactions followed by aromatizations proceeded by treating **5** and **3a** with 1,4-naphthoquinone, producing **7c** and **7m** in 65 and 85% yields. Compound **3a** reacted with maleimide (**6d**) and *N*-methylmaleimide (**6e**) to give **7e** and **7f** in 65% (dr = 1:2.3) and 72% (dr = 1:2.2) yields, respectively (entries 5 and 6). Subjecting **3a** (1 equiv) to **6b** (2 equiv) provided adduct **7g** in 83% yield in $CHCl_3$ at 62 °C for 2 h (entry 7). Exposure of **3a** to **6f** and **6j** produced the desired products **7h** (isomeric ratio=3.3:2:1) and **7i** (isomeric ratio = 2:1.8:1) in 80% and 65% yields, respectively (entries 8 and 9). Dimethyl fumarate (**6g**) and dimethyl maleate (**6h**) reacted with **3a** to give rise to adducts **7j** (75%, dr = 1:1.7) and **7k** (49%, dr = 1:3.7), respectively (entries 10 and 11). Treatment of **3a** with **6i** furnished the adduct **7l** in 70% yield (dr = 1:1.8, entry 12).



Because three isomers were produced from the reaction of **3a** with methyl vinyl ketone (**6f**), NMR spectrum of **7h** was complicated. Therefore, we tried to aromatize the Diels−Alder adducts **7h** to simplify NMR spectrum. In addition, the fact that there is not easy to introduce aromatic moieties on C4-position of 2-azetidinones led us to aromatization of adducts. Among several reaction conditions that were scrutinized, the best results were obtained with the reaction of **7h** with DBU (1 equiv) in toluene at 110 °C for 1 h, affording **8b** and **8c** (isomeric ratio = 1:4.6) in 94% yield (Table 4, entry 2). TsOH (0.8 equiv) gave the aromatic compound in 33% yield, whereas pyridine, PPTS, LDA, and DDQ did not produce the desired product. On the basis of these results, adduct **7d** was treated with DBU (1 equiv) in toluene at 110 °C, affording 2-azetidinone derivatives **8a** in 95% yield (Table 4, entry 1). Adducts **7j** and **7k**

TABLE 4. Aromatization[a]



entry	adduct	product	yield (%)[b]
1	**7d**	 **8a**	95
2	**7h**	 **8b** **8c**	94(1:4.6)[c]
3	**7j**	 **8d**	93
4	**7k**	**8d**	95
5	**7i**	 **8e** **8f**	91(1:5.5)[d]

[a] Reactions were carried out using DBU (1 equiv.) in toluene (0.1 M) at 110 °C for 1 h. [b] Isolated yield. [c] Ratio of **8b** to **8c**. [d] Ratio of **8e** to **8f**.

were aromatized to give 2-azetidinones **8d** in 93% and 95% yields, respectively (entries 3 and 4). In the case of adducts **7i**, β-lactam compounds (**8e** and **8f**) having ethyl benzoate group were produced in 91% (dr = 1:5.5) yield.

In summary, we have shown that reaction of 4-acetoxy-2-azetidinones with organoindium reagent generated in situ from indium and 1,6-dibromo-2,4-hexadiyne in the presence of LiCl in DMF produced selectively 2-azetidinones possessing 1,2,4,5-hexatetraen-3-yl group on the C4-position. The present method indicates that 1,6-dibromo-2,4-hexadiyne acts selec-tively as synthon of 3-anion of 1,2,4,5-hexatetraene. The Diels−Alder reactions of 4-(1,2,4,5-hexatetraen-3-yl)-2-azetidinones with a variety of dienophiles and subsequent aromatizations afforded valuable functional group-substituted 2-azetidinones in good yields; in this way, it serves as a new synthetic methodology of β-lactam compounds.

Experimental Section

[3*R*(1′*R*,4*S*)]-3-[1′-(tert-Butyldimethylsilyloxy)ethyl]-4-(1,2,4,5-hexatetraen-3-yl)-2-azetidinone (3a). To a suspension of indium (172.2 mg, 1.5 mmol) and lithium chloride (63.6 mg, 1.5 mmol) in DMF (1.5 mL) was added 1,6-dibromo-2,4-hexadiyne (**2**) (294.9 mg, 1.25 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 40 min, 4-acetoxy-2-azetidinone (**1**) (143.7 mg, 0.5 mmol) in DMF (0.5 mL) was added. After reaction mixture was stirred at room temperature for 3 h, the reaction mixture was poured into saturated aqueous ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), and washed with brine (20 mL). The organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane = 1/5) to afford **3a** (96.0 mg, 63%). mp = 80 °C; R_f = 0.3 (EtOAc/Hexane = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 1H), 5.75 (t, J = 5.5 Hz, 1H), 5.07−5.04 (m, 4H), 4.30 (d, J = 2.1 Hz, 1H), 4.25−4.19 (m, 1H), 3.16 (dd, J = 2.1, 3.87 Hz, 1H) 1.18 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 208.2, 169.3, 101.0, 89.8, 79.6, 79.5, 65.2, 64.6, 49.2, 26.1, 22.9, 18.3, −3.9, −4.7; IR (film) 3232, 2954, 2929, 2886, 2857, 1951, 1759, 1254, 836, 777 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{27}NO_2Si$ M^+ 305.1811, found M^+ + H 306.1895.

[[3*R*(1′*R*,4*S*)]-3-[1′-(tert-Butyldimethylsilyloxy)ethyl]-2-oxo-azetidin-4-yl]-1,4-dimethylanthraquinone (7m). The reaction mixture of **3a** (305.4 mg, 1.0 mmol) and 1,4-naphthoquinone (79.1 mg, 0.5 mmol) in chloroform (1.0 mL) was refluxed at 62 °C. After being stirred for 15 h, solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexane = 1/5) to afford **7m** (196.2 mg, 85%). mp= 233.1 °C; R_f = 0.3 (EtOAc/Hexane = 1/5);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 2H), 7.72 (m, 2H), 7.67 (s, 1H), 6.39 (s, 1H), 5.23 (d, J = 2.2 Hz, 1H), 4.35 (qd, J = 6.3, 3.1 Hz, 1H), 3.03 (dd, J = 2.2, 3.1 Hz, 1H), 2.72 (s, 3H), 2.64 (s, 3H), 1.22 (d, J = 6.3 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 185.9, 169.5, 145.6, 140.3, 137.3, 135.0, 134.8, 134.6, 134.2, 134.0, 133.9, 132.5, 126.9, 126.7, 69.4, 65.2, 49.2, 26.2, 24.3, 23.5, 18.4, 17.9, −3.9, −4.4; IR (film) 3180, 2953, 2928, 2857, 1755, 1321, 1255, 835, 720 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{33}NO_4Si$ M^+ 463.2179, found M^+ + H 464.2254.

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Supporting Information Available: Spectral data of all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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