Diels–Alder Reaction of 1,2,3-Benzotriazine with Enamine: Application to the Synthesis of Alkaloids, 2-Propylquinoline and 2-Pentylquinoline

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The Diels–Alder reaction of 1,2,3-benzotriazine with several pyrrolidine enamines of carbonyl compounds was carried out in chloroform in the presence of zinc bromide to afford 2- or 3-mono-, or 2,3-disubstituted quinolines. This method was applied to the synthesis of the alkaloids, 2-propylquinoline and 2-pentylquinoline.

Key words Diels–Alder reaction; 1,2,3-benzotriazine; quinoline derivative; 1,2,3,4-tetrahydroacridine; 2-propylquinoline; 2-pentylquinoline

Heterocyclic azadienes participate in Diels–Alder reactions with a variety of diene systems.[1] Monocyclic 1,2,3-triazines are six-membered heteroaromatics, which are so π-deficient as to react with nucleophiles.[2] We have already reported that 1,2,3-triazine undergoes an inverse-electron-demand Diels–Alder reaction with cyclic or chain ketone or aldehyde pyrrolidine enamines to afford 2- or 3-mono-, or 2,3-disubstituted pyridines.[3] We were next interested in studying the reaction of condensed-ring 1,2,3-triazine with enamines. Here, we describe the Diels–Alder reaction of 1,2,3-benzotriazine and enamines to afford the expected quinoline derivatives. In addition, we describe the synthesis of the alkaloids, 2-propylquinoline and 2-pentylquinoline, which were isolated from stems of *Galipea bracteata* (Rutaceae) and which have an inhibitory effect on shoot and root growth of lettuce.[4]

A mixture of 1,2,3-benzotriazine (**1**),[5] prepared by oxidation of 1-amino-1*H*-indazole (**2**) with lead tetraacetate, and cyclohexanone enamine (**3a**) in dry chloroform in the presence of zinc bromide was heated in a sealed glass tube at 90—100 °C for 2 h to give 1,2,3,4-tetrahydroacridine (**4a**)[6] in 35% yield from 1-amino-1*H*-indazole (**2**). 1,2,3-Benzotriazine is difficult to isolate in good yield, so it was used without purification.

We also ran the reaction with several other enamines of carbonyl compounds, and the results are summarized in Table 1. Diels–Alder reaction of **1** and the enamine of 2-butanone gave only 2-ethylquinoline (**4f**).

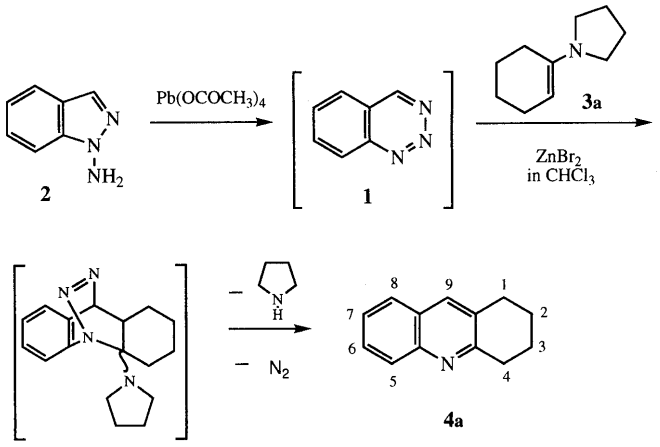
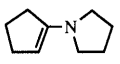
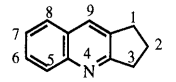
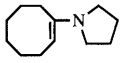
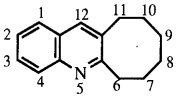
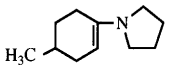
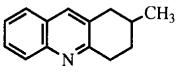
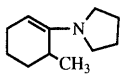
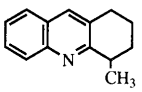
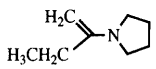
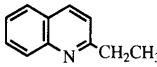
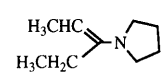
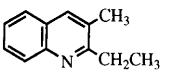
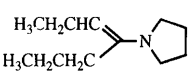
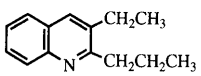
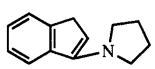
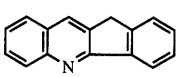
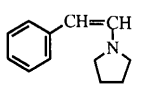
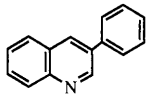


Chart 1

Treatment of 4-methyl-1,2,3-benzotriazine (**5**)[5] with the enamine **3a** by the same method gave 9-methyl-1,2,3,4-tetrahydroacridine (**6**)[15] in 25% yield.

On the basis of the above results, we carried out the synthesis of the alkaloids 2-propylquinoline (**4k-1**) and 2-pentylquinoline (**4l-1**). Diels–Alder reaction of the pyrrolidine enamine of 2-pentanone (**3k-1**) with 1,2,3-benzotriazine (**1**) gave 2-propylquinoline (**4k-1**) in 31% yield.[16] Diels–Alder reaction of 2-heptanone enamine (**3l-1**) and **1** gave 2-pentylquinoline (**4l-1**) in 35% yield.[16] Spectroscopic properties of **4k-1** and **4l-1**

Table 1. Diels–Alder Reaction of 1,2,3-Benzotriazine with Enamines

Enamine		Product		Yield (from **2**)	Ref.
	**3b**		**4b**	30%	6
	**3c**		**4c**	32%	7
	**3d**		**4d**	31%	8
	**3e**		**4e**	28%	9
	**3f**		**4f**	17%	10
	**3g**		**4g**	25%	11 12
	**3h**		**4h**	20%	12
	**3i**		**4i**	30%	13
	**3j**		**4j**	18%	14

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showed good agreement with those described in the literature.[4]

In conclusion, we have developed the synthetic method for 2- or 3-mono-, or 2,3-disubstituted quinoline derivatives by Diels–Alder reaction of 1,2,3-benzotriazine with enamines of carbonyl compounds.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined in $CDCl_3$ with Me_4Si as an internal reference on a NEVA NV-21 instrument. Mass spectra were recorded on a JEOL JMS-O1SG spectrometer. Infrared (IR) spectra were measured on a Hitachi 270-30 spectrophotometer. Preparative thin layer chromatography (PTLC) was carried out on Kiesel gel $60F_{254}$ (Merck) with appropriate solvents.

General Method for the Diels–Alder Reaction of 1,2,3-Benzotriazine (1) with Enamines A mixture of freshly prepared enamine **3a** (or **3b-l**) (1.3 eq) and 1,2,3-benzotriazine (**1**) (without purification) (prepared from **2** (100 mg)) in dry $CHCl_3$ (2 ml) was heated in a sealed glass tube at 90—100 °C for 2 h in the presence of zinc bromide (1.2 eq).[17] The solvent was evaporated *in vacuo*, and the residue was chromatographed over silica gel using C_6H_6 and $CHCl_3$ (1 : 1) as the eluent. The crude product was purified by PTLC on silica gel ($CHCl_3$: MeOH = 50 : 1) to give the corresponding quinoline derivatives as an oil or crystals.

1,2,3,4-Tetrahydroacridine (**4a**): mp 58—59 °C (MeOH) (lit.[6] 57—59 °C). IR ($CHCl_3$) cm^{-1}: 1620, 1602, 1493. ^{1}H-NMR ($CDCl_3$) δ: 1.89—1.97 (4H, m, 2-, 3-H_2), 2.98 (2H, t, J=6.5 Hz, 1-H_2), 3.13 (2H, t, J=6.5 Hz, 4-H_2), 7.43 (1H, t, J=7 Hz, 7-H), 7.63 (1H, t, J=7 Hz, 6-H), 7.68 (1H, d, J=7 Hz, 8-H), 7.80 (1H, s, 9-H), 7.96 (1H, d, J=7 Hz, 5-H). HR-MS *m/z*: 183.1060 (M$^+$, Calcd for $C_{13}H_{13}N$: 183.1048).

2,3-Dihydro-1*H*-cyclopenta[*b*]quinoline (**4b**): mp 51 °C (MeOH) (lit.[6] 53 °C). IR ($CHCl_3$) cm^{-1}: 1622, 1572, 1498. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (2H, t, J=7.5 Hz, 2-H_2), 3.09 (2H, t, J=7.5 Hz, 1-H_2), 3.17 (2H, t, J=7.5 Hz, 3-H_2), 7.45 (1H, t, J=8 Hz, 7-H), 7.62 (1H, t, J=8 Hz, 6-H), 7.73 (1H, d, J=8 Hz, 8-H), 7.89 (1H, s, 9-H), 8.01 (1H, d, J=8 Hz, 5-H). HR-MS *m/z*: 169.0893 (M$^+$, Calcd for $C_{12}H_{11}N$: 169.0891).

6,7,8,9,10,11-Hexahydrocycloocta[*b*]quinoline (**4c**): mp 53—55 °C (MeOH) (lit.[7] 59 °C). IR ($CHCl_3$) cm^{-1}: 1601, 1494. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (4H, m, 8-, 9-H_2), 1.84 (4H, m, 7-, 10-H_2), 2.95 (2H, m, 11-H_2), 3.17 (2H, m, 6-H_2), 7.45 (1H, t, J=8 Hz, 2-H), 7.62 (1H, t, J=8 Hz, 3-H), 7.73 (1H, d, J=8 Hz, 1-H), 7.84 (1H, s, 12-H), 8.05 (1H, d, J=8 Hz, 4-H). HR-MS *m/z*: 211.1369 (M$^+$, Calcd for $C_{15}H_{17}N$: 211.1360).

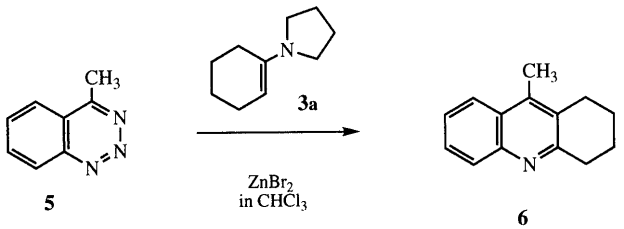

Chart 2

2-Methyl-1,2,3,4-tetrahydroacridine (**4d**): Oil. IR ($CHCl_3$) cm^{-1}: 1622, 1604, 1495. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.5 Hz, CH_3), 1.62 (1H, m, 2-H), 2.04 (2H, m, 3-H_2), 2.60 (1H, m, 1-H), 3.13 (3H, m, 1-H, 4-H_2), 7.43 (1H, t, J=8 Hz, 7-H), 7.61 (1H, t, J=8 Hz, 6-H), 7.70 (1H, d, J=8 Hz, 8-H), 7.80 (1H, s, 9-H), 7.98 (1H, d, J=8 Hz, 5-H). HR-MS *m/z*: 197.1215 (M$^+$, Calcd for $C_{14}H_{15}N$: 197.1204).

4-Methyl-1,2,3,4-tetrahydroacridine (**4e**): Oil. IR ($CHCl_3$) cm^{-1}: 1620, 1492. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7 Hz, CH_3), 2.10 (3H, m, 2-H_2, 3-H), 2.96 (2H, m, 1-H, 3-H), 3.21 (1H, m, 1-H), 3.55 (1H, m, 4-H), 7.42 (1H, t, J=8 Hz, 7-H), 7.60 (1H, t, J=8 Hz, 6-H), 7.69 (1H, d, J=8 Hz, 8-H), 7.79 (1H, s, 9-H), 8.00 (1H, d, J=8 Hz, 5-H). HR-MS *m/z*: 197.1207 (M$^+$, Calcd for $C_{14}H_{15}N$: 197.1204).

2-Ethylquinoline (**4f**): Oil. IR ($CHCl_3$) cm^{-1}: 1619, 1602, 1505. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.5 Hz, CH_3), 3.01 (2H, q, J=7.5 Hz, CH_2), 7.31 (1H, d, J=8 Hz, 3-H), 7.47 (1H, t, J=8 Hz, 6-H), 7.68 (1H, t, J=8 Hz, 7-H), 7.76 (1H, d, J=8 Hz, 5-H), 8.06 (2H, t-like, J=8 Hz, 4-, 8-H). HR-MS *m/z*: 157.0903 (M$^+$, Calcd for $C_{11}H_{11}N$: 157.0891).

2-Ethyl-3-methylquinoline (**4g**): Oil. IR ($CHCl_3$) cm^{-1}: 1604, 1495. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.5 Hz, CH_3), 2.49 (3H, s, CH_3), 3.00 (2H, q, J=7.5 Hz, CH_2), 7.44 (1H, t, J=8 Hz, 6-H), 7.61 (1H, t, J=8 Hz, 7-H), 7.70 (1H, d, J=8 Hz, 5-H), 7.84 (1H, s, 4-H), 8.02 (1H, d, J=8 Hz, 8-H). HR-MS *m/z*: 171.1066 (M$^+$, Calcd for $C_{12}H_{13}N$: 171.1048).

3-Ethyl-2-propylquinoline (**4h**): Oil. IR ($CHCl_3$) cm^{-1}: 1603, 1492. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7.5 Hz, CH_3), 1.35 (3H, t, J=8 Hz, CH_3), 1.82 (2H, m, CH_2), 2.90 (4H, m, $CH_2 \times 2$), 7.45 (1H, t, J=8 Hz, 6-H), 7.62 (1H, t, J=8 Hz, 7-H), 7.74 (1H, d, J=8 Hz, 5-H), 7.88 (1H, s, 4-H), 8.05 (1H, d, J=8 Hz, 8-H). HR-MS *m/z*: 199.1361 (M$^+$, Calcd for $C_{14}H_{17}N$: 199.1360).

11H-Indeno[1,2-*b*]quinoline (**4i**): mp 165—168 °C (MeOH) (lit.[13] 167—168 °C). IR ($CHCl_3$) cm^{-1}: 1628, 1568, 1504. ^{1}H-NMR ($CDCl_3$) δ: 4.05 (2H, s, CH_2), 7.41—7.86 (6H, m, aromatic-H), 8.12—8.34 (3H, m, aromatic-H). HR-MS *m/z*: 217.0888 (M$^+$, Calcd for $C_{16}H_{11}N$: 217.0890).

3-Phenylquinoline (**4j**): Oil. IR ($CHCl_3$) cm^{-1}: 1599, 1580, 1495. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.62 (4H, m, aromatic-H), 7.67—7.76 (3H, m, aromatic-H), 7.88 (1H, d, J=8 Hz, 5-H), 8.14 (1H, d, J=8 Hz, 8-H), 9.18 (1H, s, 4-H), 9.31 (1H, s, 2-H). HR-MS *m/z*: 205.0907 (M$^+$, Calcd for $C_{15}H_{11}N$: 205.0891).

9-Methyl-1,2,3,4-tetrahydroacridine (**6**): This compound was prepared by general method from benzotriazine **5** and the enamine **3a** in 25% yield from **2**. mp 72—73 °C (MeOH) (lit.[15] 71—72.5 °C). IR ($CHCl_3$) cm^{-1}: 1613, 1582. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (4H, m, 2-, 3-H_2), 2.54 (3H, s, CH_3), 2.90 (2H, m, 1-H_2), 3.12 (2H, m, 4-H_2), 7.40—7.70 (2H, m, 6-, 7-H), 7.97 (2H, d, J=8 Hz, 5-, 8-H). HR-MS *m/z*: 197.1216 (M$^+$, Calcd for $C_{14}H_{15}N$: 197.1204).

2-Propylquinoline (**4k-1**): Oil. IR ($CHCl_3$) cm^{-1}: 1618, 1601, 1561, 1504. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7.5 Hz, CH_3), 1.84 (2H, m, CH_2), 2.94 (2H, t, J=7.5 Hz, CH_2), 7.26 (1H, d, J=8.4 Hz, 3-H), 7.45 (1H, t, J=8 Hz, 6-H), 7.66 (1H, t, J=8 Hz, 7-H), 7.74 (1H, t, J=8 Hz, 5-H), 8.02 (1H, d, J=8 Hz, 8-H), 8.06 (1H, d, J=8.4 Hz, 4-H). HR-MS *m/z*: 171.1056 (M$^+$, Calcd for $C_{12}H_{13}N$: 171.1047).

2-Pentylquinoline (**4l-1**): Oil. IR ($CHCl_3$) cm^{-1}: 1618, 1601, 1560, 1505, 1458, 1426. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7 Hz, CH_3), 1.36 (4H, m, $CH_2 \times 2$), 1.81 (2H, m, CH_2), 2.95 (2H, t, J=7 Hz, CH_2), 7.26

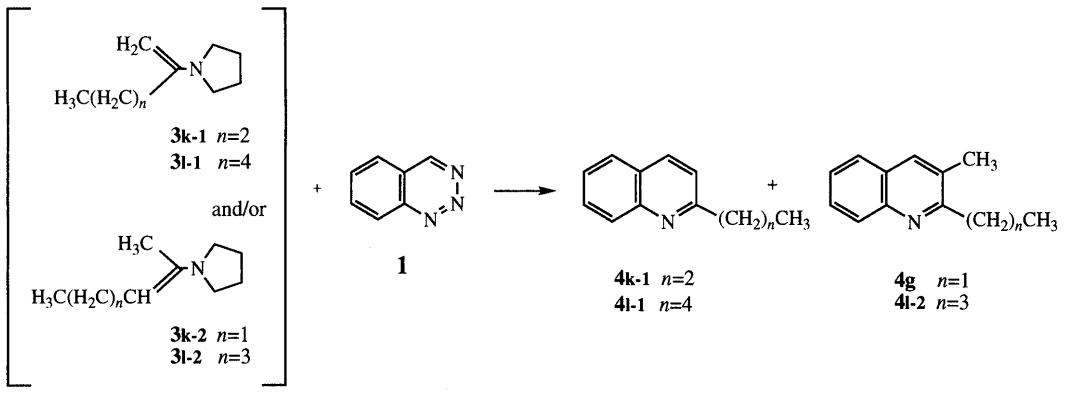

Chart 3

(1H, d, J=8.5 Hz, 3-H), 7.44 (1H, t, J=8 Hz, 6-H), 7.64 (1H, t, J=8 Hz, 7-H), 7.73 (1H, t, J=8 Hz, 5-H), 8.00 (1H, d, J=8 Hz, 8-H), 8.05 (1H, d, J=8.5 Hz, 4-H). HR-MS m/z: 199.1355 (M^+, Calcd for $C_{14}H_{17}N$: 199.1360).

2-Butyl-3-methylquinoline (**4l-2**): Oil. IR ($CHCl_3$) cm^{-1}: 1604, 1565, 1460. ^1H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7 Hz, CH_3), 1.44—1.72 (4H, m, $CH_2 \times 2$), 2.73 (3H, s, CH_3), 2.76 (2H, t, J=7.3 Hz, CH_2), 7.44 (1H, t, J=8 Hz, 6-H), 7.61 (1H, t, J=8 Hz, 7-H), 7.72 (1H, d, J=8 Hz, 5-H), 7.83 (1H, s, 4-H), 8.00 (1H, d, J=8 Hz, 8-H). HR-MS m/z: 199.1364 (M^+, Calcd for $C_{14}H_{17}N$: 199.1360).

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16) The 2-pentanone enamine was prepared from 2-pentanone and pyrrolidine in benzene in the presence of *p*-toluenesulfonic acid for about 1 h. The Diels–Alder reaction of **1** and the above enamine gave **4k-1**, but **4g** could not be detected by TLC. The reaction of 2-heptanone enamine (reaction time: 1 h) and **1** gave only **4l-1**. The preparation time of enamines (of 2-pentanone or 2-heptanone) was over 10 h, so that the Diels–Alder reaction of **1** and enamines gave **4k-1** or **4l-1** as the main product (30, 32%) and **4g** or **4l-2** as the minor product (5, 9%). The Diels–Alder reaction of **3f** and **1** gave only **4f** whether the preparation time of enamine was short or long.
17) The catalyst, zinc bromide, is necessary for the Diels–Alder reaction of aldehyde enamines and triazine derivatives.[3c] But the yields of the Diels–Alder reaction of **1** and the enamines of other carbonyl compounds were rather similar in the presence and in the absence of zinc bromide.