Pergamon

Tetrahedron 57 (2001) 2015–2019

TETRAHEDRON

Regioselective synthetic approaches towards 1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-ones

A. S. Girgis,[a] Y. A. Ibrahim,[b] N. Mishriky,[a,*] J. N. Lisgarten,[c] B. S. Potter[c] and R. A. Palmer[c]

[a]*National Research Centre, Dokki, Cairo, Egypt*
[b]*Department of Chemistry, Faculty of Science, Cairo University, Ciza, Egypt*
[c]*Department of Crystallography, Birkbeck College, University of London, Malet Street, London WCIE 7HX, UK*

Received 4 September 2000; revised 28 November 2000; accepted 21 December 2000

Abstract—1,3-Dipolar cycloaddition of 2,6-bis(arylmethylidene)cyclohexanones **1** to a variety of nitrilimines (generated in situ by triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2**) proceeded regioselectively affording 1,3,4,8,10,11-hexaaryl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-ones as a mixture of two isomers **3** and **4**. The structures of which were established by different spectroscopic techniques as well as single crystal X-ray diffraction.

1. Introduction

Spiro-compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[1–3] The most developed phenomenon for the synthesis of these compounds depends mainly on cycloaddition reaction to exocyclic double bonds.[4–8] 1,3-Dipolar cycloaddition reactions are considered the most successful process for the construction of five-membered ring containing spiro compounds due to high regio- and stereoselective properties of these reactions.[9]

In the present work, it is intended to investigate the reactions of a variety of nitrilimines with a number of 2,6-bis(arylmethylidene)cyclohexanones **1** attempting not only to study the regioselectivity of the reactions but also to isolate the corresponding tetraazadispiro compounds.

2. Results and discussion

Reaction of 2,6-bis(arylmethylidene)cyclohexanones **1** with nitrilimines (generated in situ by triethylamine dehydrohalogenation of the corresponding hydrazonoyl chlorides **2**) in refluxing dry benzene, afforded 1,3,4,8,10,11-hexaaryl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-ones as a mixture of two isomers **3** and **4**. The structures of which were established by different spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR), elemental analyses and single crystal X-ray diffraction.

The IR spectra of **3** reveal the presence of a carbonyl stretching vibration band at 1712–1705 cm^{-1}. Similarly, **4** exhibits a strong carbonyl absorption band at 1725–1697 cm^{-1} region excluding any cycloaddition reaction with this function. The ^{1}H NMR spectra reveal a singlet signal at δ 4.91–5.04 and 3.92–3.97 in case of **3** and **4**, respectively, assignable to the chemically and magnetically equivalent H-4 and H-11 in each case. The absence of any signal downfield of δ 5.6 exclude the presence of any other regioisomer like **5** or **6**.[10–13]

^{13}C NMR spectra of **3** and **4** add conclusive support for the proposed structures. They exhibit the presence of the equivalent methine carbons (C-4, C-11) at δ 61.9 and 59.9 and the equivalent spiro carbons (C-5, C-7) at δ 81.2 and 79.0 in case of **3e** and **4e**, respectively (cf. Section 3). These observed chemical shift values are consistent with many other similar structures.[12,13]

From all the above data, it is obvious that the reaction occurs regioselectively via cycloaddition of two moles of nitrilimines to **1** from either the same face giving rise to the cycloadducts **3** or from opposite faces affording the isomeric products **4**. Single crystal X-ray diffraction of **4e** (Fig. 1)[14] add a sharp evidence for this assumption which clearly exhibit the cycloaddition coming from attack of nitrilimines to the olefinic linkages at opposite faces. Attempts to perform X-ray crystallography of **3** were unsuccessful due to difficulty in obtaining appropriate crystals of this material in suitable form.

The ^{1}H NMR upfield shift of the methine pyrazole protons (H-4, H-11) in compound **4** compared with **3** could be attributed to the anisotropic effect (shielding effect) of the aryl group attached to the corresponding pyrazole nitrogens

Keywords: 2,6-bis(arylmethylidene)cyclohexanones; hydrazonoyl chlorides; 1,3-dipolar cycloaddition.
* Corresponding author

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00020-5

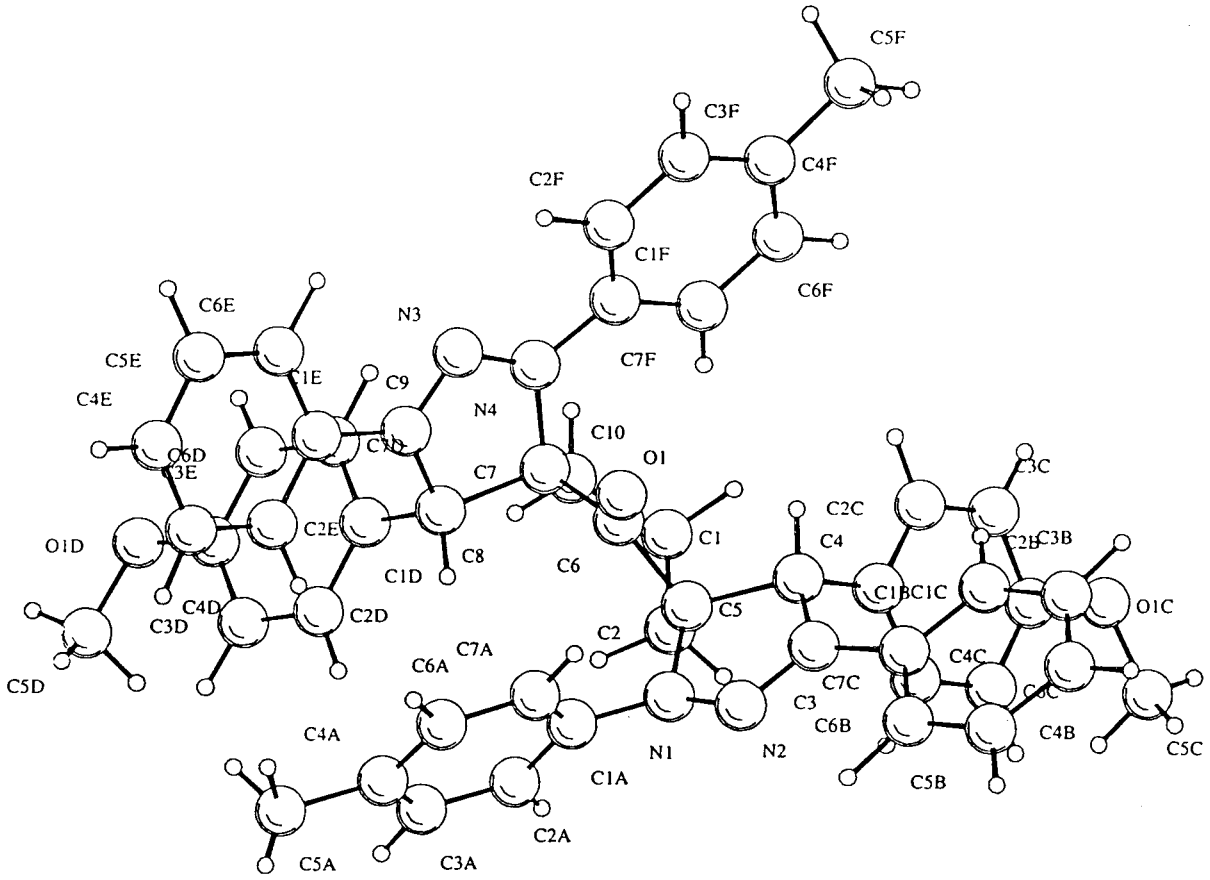


Figure 1. Single crystal X-ray diffraction of **4e**.

(N-8 and N-1, respectively). Single crystal X-ray diffraction supports this assumption (cf. Fig. 1)

3. Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin–Elmer 1650 spectrophotometer. ^{1}H and ^{13}C NMR (on-resonance and APT) spectra were recorded on a Varian GEMINI 200 (^{1}H: 200; ^{13}C: 50 MHz). The starting compounds **1**[15] were prepared according to the reported procedures (Scheme 1)

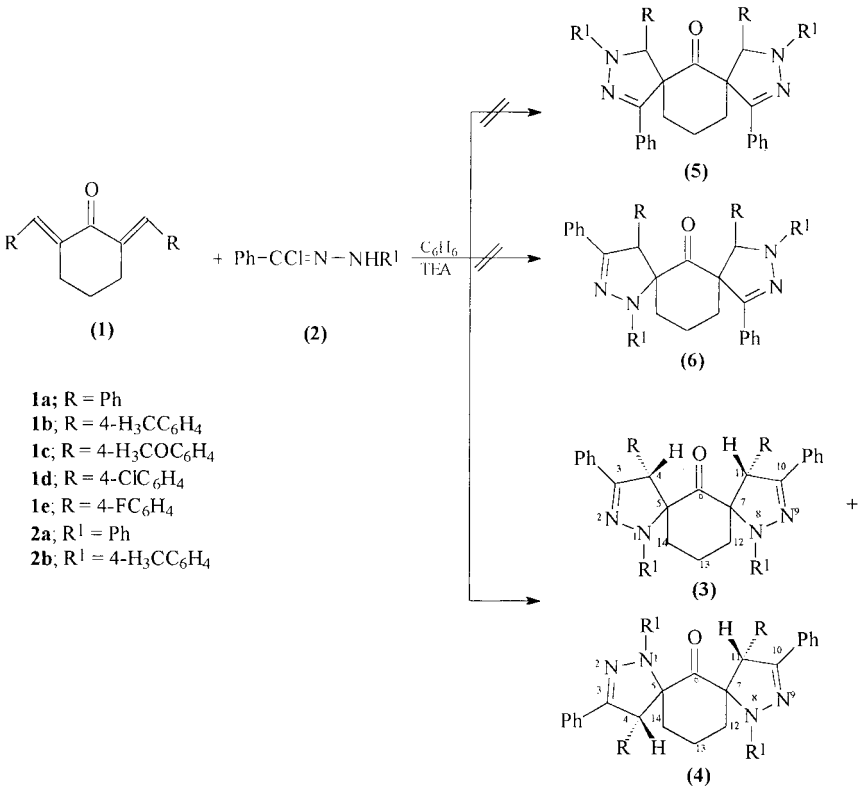
For X-ray crystallography, compound **4e** was recrystallized as yellow crystals from *n*-butanol. Preliminary Weissenberg photographs were used to derive approximate cell dimensions, Laue symmetry, possible space groups, and to check crystal quality. A suitable crystal was mounted on a CAD4 automated diffractometer. CAD4 EXPRESS'88 software[16] was used for unit cell determination and refinement, data collection, and data reduction. Accurate cell parameters were determined from 25 reflections ($25<\theta<28°$) employing graphite monochromated CuK_{α} radiation with $\omega-2\theta$ scans. Intensities of 8216 reflections were measured for $\theta<70°$. The crystal showed no significant variation in intensities of three check reflections during the course of data collection. Lorentz and polarization corrections were applied but absorption effects were ignored.

The structure was solved using SHELX-86[17] and refined using SHELX-93.[17] Geometrical calculations were made with SHELX-93[18] and the same software was used to prepare publication material and tables. The program SNPI[19] was used to prepare the structure drawings. Hydrogen atoms were refined in riding mode with isotopic temperature factors. Calculations were performed on a PC486 computer.

The chemical formula and ring labelling system is shown in Fig. 1. Full X-ray data are provided separately as supplementary materials.[14]

3.1. Reaction of 2,6-bis(arylmethylidene)cyclohexanones 1 with hydrazonoyl chlorides 2: General procedure

A mixture of **1** (2.5 mmol) and the appropriate hydrazonoyl chloride **2** (5 mmol) in dry benzene (30 mL) containing triethylamine (7.5 mmol) was boiled under reflux for the appropriate time. The reaction mixture was filtered while hot to remove the triethylamine hydrochloride, then concentrated to 10 mL and cooled overnight (10°C). The separated solid was collected and crystallized from a suitable solvent affording the corresponding **3**. In the case of **3c** after concentrating the reaction mixture to about 10 mL, light petroleum (60–80°C; 10 mL) was added. Thus, **3c** which separated was collected and treated as above. The remaining mother liquor was evaporated to dryness under reduced pressure and after triturating the residue with methanol (5 mL), a solid separated which was collected and crystallized from a suitable solvent affording the corresponding **4**.



Compd	R	R1	3	4
a	Ph	Ph	40%	46%
b	Ph	4-$H_3CC_6H_4$	39%	33%
c	4-$H_3CC_6H_4$	Ph	33%	39%
d	4-$H_3COC_6H_4$	Ph	32%	38%
e	4-$H_3COC_6H_4$	4-$H_3CC_6H_4$	37%	37%
f	4-ClC_6H_4	Ph	37%	32%
g	4-FC_6H_4	Ph	33%	39%
h	4-FC_6H_4	4-$H_3CC_6H_4$	38%	—

Scheme 1.

3.1.1. 1,3,4,8,10,11-Hexaphenyl-1,2,8,9-tetraazadispiro-[4.1.4.3]tetradeca-2,9-dien-6-one. (**3a**): Reaction time 60 h; almost colourless crystals from *n*-butanol; mp 309–311°C; yield 40% (Found: C, 83.00; H, 5.82; N, 8.63. $C_{46}H_{38}N_4O$ requires C, 83.35; H, 5.78; N, 8.45%); ν_{max} 1708 cm^{-1} (CO); 1591, 1562 (C=N, C=C). δ_H ($CDCl_3$) 1.26–2.58 (m, 6H, $3CH_2$); 5.04 (s, 2H, H-4+H-11); 6.92–7.57 (m, 30H, arom. H).

(**4a**): Yellow crystals from *n*-butanol; mp 281–283°C; yield 46% (Found: C, 83.22; H, 5.99; N, 8.09. $C_{46}H_{38}N_4O$ requires C, 83.35; H, 5.78; N, 8.45%); ν_{max} 1702 cm^{-1} (CO); 1591, 1488 (C=N, C=C). δ_H ($CDCl_3$) 1.33–2.27 (m, 6H, $3CH_2$); 3.97 (s, 2H, H-4+H-11); 7.14–7.44 (m, 30H, arom. H).

3.1.2. 1,8-Bis(4-methylphenyl)-3,4,10,11-tetraphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3b**): Reaction time 65 h; pale yellow crystals from *n*-butanol; mp 287–289°C; yield 39% (Found: C, 83.12; H, 6.41; N, 7.98. $C_{48}H_{42}N_4O$ requires C, 83.45; H, 6.13; N, 8.11%); ν_{max} 1712 cm^{-1} (CO); 1589, 1559 (C=N, C=C). δ_H ($CDCl_3$) 1.20–2.25 (m, 6H, $3CH_2$); 2.29 (s, 6H, $2CH_3$); 4.96 (s, 2H, H-4+H-11); 6.81–7.54 (m, 28H, arom. H).

(**4b**): Yellow crystals from *n*-butanol; mp 257–259°C; yield 33% (Found: C, 83.62; H, 6.40; N, 8.41. $C_{48}H_{42}N_4O$ requires C, 83.45; H, 6.13; N, 8.11%); ν_{max} 1725 cm^{-1} (CO); 1604, 1507 (C=N, C=C). δ_H ($CDCl_3$) 1.27–2.30 (m, 6H, $3CH_2$); 2.38 (s, 6H, $2CH_3$); 3.94 (s, 2H, H-4+H-11); 7.13–7.36 (m, 28H, arom. H).

3.1.3. 4,11-Bis(4-methylphenyl)-1,3,8,10-tetraphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3c**): Reaction time 60 h; colourless crystals from *n*-butanol; mp 290–292°C; yield 33% (Found: C, 83.71; H, 6.43; N, 8.49. $C_{48}H_{42}N_4O$ requires C, 83.45; H, 6.13; N, 8.11%); ν_{max} 1710 cm^{-1} (CO); 1591, 1562 (C=N, C=C). δ_H ($CDCl_3$) 1.25–2.30 (m, 6H, $3CH_2$); 2.38 (s, 6H, $2CH_3$); 4.95 (s, 2H, H-4+H-11); 6.95–7.60 (m, 28H, arom. H).

(**4c**): Yellow crystals from *n*-butanol; mp 290–292 °C; yield 39% (Found: C, 83.19; H, 5.97; N, 8.18. $C_{48}H_{42}N_4O$ requires C, 83.45; H, 6.13; N, 8.11%); ν_{max} 1697 cm^{-1} (CO); 1592, 1488 (C═N, C═C). δ_H ($CDCl_3$) 1.35–2.25 (m, 6H, $3CH_2$); 2.30 (s, 6H, $2CH_3$); 3.97 (s, 2H, H-4+H-11); 6.90–7.50 (m, 28H, arom. H).

3.1.4. 4,11-Bis(4-methoxyphenyl)-1,3,8,10-tetraphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3d**): Reaction time 55 h; almost colourless crystals from *n*-butanol; mp 273–275°C; yield 32% (Found: C, 80.01; H, 5.78; N, 7.57. $C_{48}H_{42}N_4O_3$ requires C, 79.75; H, 5.86; N, 7.75%); ν_{max} 1705 cm^{-1} (CO); 1592, 1511 (C═N, C═C). δ_H ($CDCl_3$) 1.30–2.30 (m, 6H, $3CH_2$); 3.84 (s, 6H, $2OCH_3$); 4.95 (s, 2H, H-4+H-11); 6.93–7.56 (m, 28H, arom. H).

(**4d**): Yellow crystals from *n*-butanol; mp 264–265°C; yield 38% (Found: C, 79.98; H, 6.03; N, 8.04. $C_{48}H_{42}N_4O_3$ requires C, 79.75; H, 5.86; N, 7.75%); ν_{max} 1706 cm^{-1} (CO); 1595, 1509 (C═N, C═C). δ_H ($CDCl_3$) 1.38–2.25 (m, 6H, $3CH_2$); 3.76 (s, 6H, $2OCH_3$); 3.93 (s, 2H, H-4+H-11); 6.75–7.45 (m, 28H, arom. H).

3.1.5. 4,11-Bis(4-methoxyphenyl)-1,8-bis(4-methylphenyl)-3,10-diphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3e**): Reaction time 60 h; almost colourless crystals from *n*-butanol; mp 284–286°C; yield 37% (Found: C, 80.31; H, 5.99; N, 7.87. $C_{50}H_{46}N_4O_3$ requires C, 79.97; H, 6.18; N, 7.46%); ν_{max} 1707 cm^{-1} (CO); 1609, 1561 (C═N, C═C). δ_H ($CDCl_3$) 1.25–2.25 (m, 6H, $3CH_2$); 2.29 (s, 6H, $2CH_3$); 3.83 (s, 6H, $2OCH_3$); 4.92 (s, 2H, H-4+H-11); 6.80–7.55 (m, 26H, arom. H). δ_C ($CDCl_3$) 19.2, 29.3 (CH_2); 20.5 (CH_3); 55.2 (OCH_3); 61.9 (C-4, C-11); 81.2 (spiro-C); 122.0, 126.1, 128.0, 128.3, 129.1, 130.9, 131.0, 131.1, 131.2 (arom. CH); 126.6, 132.3, 140.3, 147.9 (arom. quaternary C); 159.8 (C═N); 202.7 (CO).

(**4e**): Yellow crystals from *n*-butanol; mp 235–237°C; yield 37% (Found: C, 80.09; H, 6.02; N, 7.35. $C_{50}H_{46}N_4O_3$ requires C, 79.97; H, 6.18; N, 7.46%); ν_{max} 1702 cm^{-1} (CO); 1605, 1508 (C═N, C═C). δ_H ($CDCl_3$) 1.29–2.26 (m, 6H, $3CH_2$); 2.39 (s, 6H, $2CH_3$); 3.76 (s, 6H, $2OCH_3$); 3.92 (s, 2H, H-4+H-11); 6.81–7.38 (m, 26H, arom. H). δ_C ($CDCl_3$) 17.5, 27.7 (CH_2); 20.7 (CH_3); 55.1 (OCH_3); 59.9 (C-4, C-11); 79.0 (spiro-C); 122.5, 126.4, 128.0, 128.2, 129.7, 130.8 (arom. CH); 127.2, 132.0, 133.4, 142.5, 151.0 (arom. quaternary C); 159.4 (C═N); 205.3 (CO).

3.1.6. 4,11-Bis(4-chlorophenyl)-1,3,8,10-tetraphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3f**): Reaction time 55 h; almost colourless crystals from *n*-butanol; mp 310–312°C; yield 37% (Found: C, 75.31; H, 5.23; N, 7.94. $C_{46}H_{36}Cl_2N_4O$ requires C, 75.50; H, 4.96; N, 7.66%); ν_{max} 1710 cm^{-1} (CO); 1593, 1564 (C═N, C═C). δ_H ($CDCl_3$) 1.15–2.35 (m, 6H, $3CH_2$); 4.93 (s, 2H, H-4+H-11); 6.92–7.51 (m, 28H, arom. H).

(**4f**): Yellow crystals from *n*-butanol; mp 285–287°C; yield 32% (Found: C, 75.42; H, 4.83; N, 7.59. $C_{46}H_{36}Cl_2N_4O$ requires C, 75.50; H, 4.96; N, 7.66%); ν_{max} 1698 cm^{-1} (CO); 1593, 1489 (C═N, C═C). δ_H ($CDCl_3$) 1.39–2.26 (m, 6H, $3CH_2$); 3.92 (s, 2H, H-4+H-11); 6.90–7.45 (m, 28H, arom. H).

3.1.7. 4,11-Bis(4-fluorophenyl)-1,3,8,10-tetraphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3g**): Reaction time 40 h; almost colourless crystals from *n*-butanol; mp 313–315°C; yield 33% (Found; C, 79.33; H, 5.41; N, 7.88. $C_{46}H_{36}F_2N_4O$ requires C, 79.06; H, 5.19; N, 8.02%); ν_{max} 1709 cm^{-1} (CO); 1595, 1564 (C═N, C═C). δ_H ($CDCl_3$) 1.20–2.35 (m, 6H, $3CH_2$); 4.95 (s, 2H, H-4+H-11); 6.92–7.54 (m, 28H, arom. H).

(**4g**): Yellow crystals from *n*-butanol; mp 282–284°C; yield 39% (Found: C, 79.44; H, 5.01; N, 7.94. $C_{46}H_{36}F_2N_4O$ requires C, 79.06; H, 5.19; N, 8.02%); ν_{max} 1699 cm^{-1} (CO); 1598, 1506 (C═N, C═C). δ_H ($CDCl_3$) 1.38–2.26 (m, 6H, $3CH_2$); 3.94 (s, 2H, H-4+H-11); 6.99–7.45 (m, 28H, arom. H).

3.1.8. 4,11-Bis(4-fluorophenyl)-1,8-bis(4-methylphenyl)-3,10-diphenyl-1,2,8,9-tetraazadispiro[4.1.4.3]tetradeca-2,9-dien-6-one. (**3h**): Reaction time 75 h; pale yellow crystals from *n*-butanol; mp 308–310°C; yield 38% (Found: C, 79.72; H, 5.79; N, 7.83. $C_{48}H_{40}F_2N_4O$ requires C, 79.31; H, 5.55; N, 7.71%); ν_{max} 1710 cm^{-1} (CO); 1603, 1561 (C═N, C═C). δ_H ($CDCl_3$) 1.20–2.25 (m, 6H, $3CH_2$); 2.30 (s, 6H, $2CH_3$); 4.91 (s, 2H, H-4+H-11); 6.80–7.52 (m, 28H, arom. H).

References

1. Longeon, A.; Guyot, M.; Vacelet, J. *Experentia* **1990**, *46*, 548.
2. Kobayashi, J.; Tsuda, M.; Agemi, K.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *Tetrahedron* **1991**, *47*, 6617.
3. James, D. M.; Kunze, H. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1137.
4. Fisera, L.; Sauter, F.; Frohlich, J.; Feng, Y.; Ertl, P.; Mereiter, K. *Monatsh. Chem.* **1994**, *125*, 553.
5. Fisera, L.; Sauter, F.; Frohlich, J.; Feng, Y.; Mereiter, K. *Monatsh. Chem.* **1994**, *125*, 909.
6. Strauss, A.; Otto, H. H. *Helv. Chim. Acta* **1997**, *80*, 1823.
7. Stverkova, S.; Zak, Z.; Jonas, J. *Liebigs Ann. Chem.* **1995**, 477.
8. Mishriky, N.; Asaad, F. M.; Ibrahim, Y. A.; Girgis, A. S. *J. Chem. Res. Synop.* **1997**, 438.
9. Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*, Wiley: New York, 1984; Vol. 1, pp 291.
10. Anelli, P. L.; Croce, P. D. *Gazz. Chim. Ital.* **1981**, *111*, 269.
11. Abdallah, M. A.; Albar, H. A.; Shawali, A. S. *J. Chem. Res. Synop.* **1993**, 182.
12. Fathi, T.; Ciamala, K.; Dinh An, N.; Vebrel, J. *Can. J. Chem.* **1994**, *72*, 1424.
13. Mishriky, N.; Girgis, A. S.; Ibrahim, Y. A. *J. Chem. Res. Synop.* **2000**, 2.
14. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 152424. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

15. (a) Vorländer, D.; Kunze, K. *Ber.* **1926**, *59B*, 2078. (b) Garland, C. E.; Reid, E. E. *J. Am. Chem. Soc.* **1925**, *47*, 2333. (c) Müller, A. *Ber.* **1921**, *54B*, 1481. (d) Huitric, A. C.; Kumler, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 614. (e) Buu-Hoi, Ng. Ph.; Xuong, N. D.; Rips, R. *J. Org. Chem.* **1957**, *22*, 193.
16. Enraf-Nonius CAD-4 EXPRESS'88 Software, Enraf-Nonius, Delft, Holand.
17. Sheldrick, G. M. *SHELX86: Program for Crystal Structure Determination*; University of Göttingen, Germany, 1986.
18. Sheldrick, G. M. *SHELX93: Program for Crystal Structure Refinement*; University of Göttingen, Germany, 1993.
19. Karaulov, A. *SNPI: Molecular Plotting Programme*; School of Chemistry and Applied Chemistry, University of Wales, Cardiff, 1994.