Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

Synthesis of Triazolyl-Substituted Quinolizidine Imides

Shang-Shing P. Chou,* Chang-Lin Lu and Yen-Hao Hsu
Department of Chemistry, Fu Jen Catholic University, Taipei, Taiwan 242, R.O.C.

(Received: Oct. 17, 2011; Accepted: Nov. 16, 2011; Published Online: Nov. 29, 2011; DOI: 10.1002/jccs.201100610)

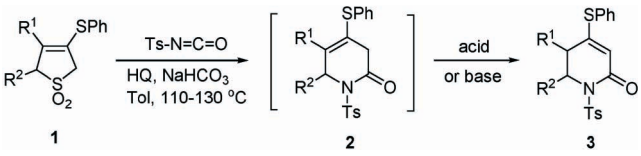
Some bicyclic imides and triazole compounds have separately shown biological activities. We now combine these two structural features into the synthesis of triazolyl-substituted quinolizidine imides **21**. Dihydro-2-pyridone compound **15**, obtained previously from the aza-Diels-Alder reaction, was first oxidized to the sulfone **16** which was effectively converted to the azide **17**. Further click chemistry of compound **17** with terminal alkynes provided regiospecifically the 1,4-disubstituted triazoles **18a**-**c**. Sequential detosylation with Bu_3SnH/AIBN, *N*-allylation and ring-closing metathesis (RCM) reaction then provided the bicyclic imides **21a**-**b**.

Keywords: Aza-Diels-Alder reactions; Click chemistry; Dihydro-2-pyridones; Ring-closing metathesis (RCM); Quinolizidines; Imides.

INTRODUCTION

Many natural and synthetic compounds bearing the piperidine ring often exhibit interesting biological activities.[1] Various methods have been developed to synthesize these compounds.[2] The aza-Diels-Alder reaction is one of the most versatile routes to construct the piperidine structure.[3] We have previously reported that thio-substituted 3-sulfolenes **1** can undergo *in situ* thermal desulfonylation and subsequent cycloaddition reaction with *p*-toluenesulfonyl isocyanate (PTSI) to give the cyclized products **2**. Further treatment with acid or base can yield the conjugated dihydro-2-pyridones **3** (Scheme I).[4] We have reported some synthetic applications of this method,[5] and have studied some of their biological activities.[6]

Scheme I Synthesis of 4-(phenylthio)-5,6-dihydro-2-pyridones **3**

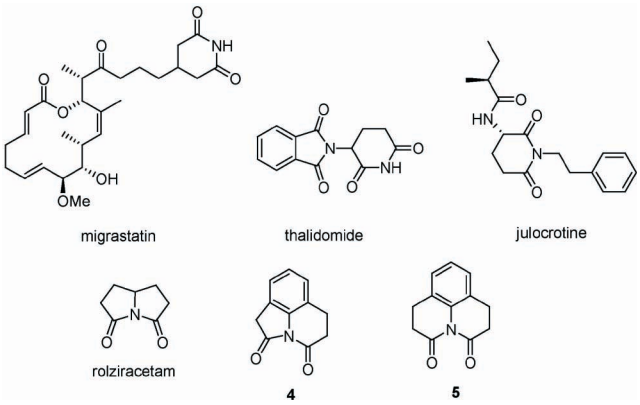


1 2 3

It has been reported that cyclic imides such as migrastatin,[7] thalidomide,[8] and julocrotine[9] have very useful biological activities. Some bicyclic imides including rolziracetam[10] and benzo-fused compounds **4** and **5** have the potential for treating Alzheimer's disease (Scheme II).[11]

A new idea of "click chemistry" was introduced by Sharpless as a set of modular reactions for the rapid synthesis of combinatorial libraries especially through heteroatom links (C–X–C),[12] and has been widely applied to drug synthesis[13] and materials science.[14] Among these nearly perfect "spring-loaded" reactions, probably the most widely used reaction is the azide-alkyne cycloaddition catalyzed by Cu(I) (abbreviated as CuAAC) giving the 1,4-disubstituted triazoles.[15] We would like to report that we can combine our aza-Diels-Alder reaction method and the click chemistry to synthesize a series of triazolyl-substituted quinolizidine imides, hopefully with unusual biological activities.

Scheme II Some biologically active cyclic imides



RESULTS AND DISCUSSION

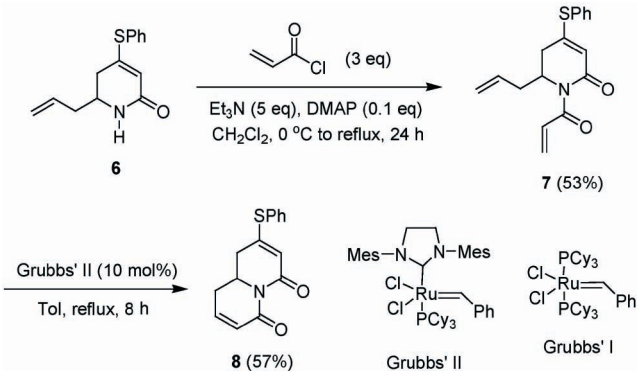
Starting from 6-allyl-4-(phenylthio)-5,6-dihydro-2-

Dedicated to the memory of Professor Yung-Son Hon (1955–2011).

* Corresponding author. E-mail: chem1004@mails.fju.edu.tw

pyridone (**6**),[5a] after experimenting some reaction conditions, a fair yield of compound **7** was obtained by reacting with acryloyl chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) in refluxing CH_2Cl_2. If NaH or BuLi was used as the base, the yield of compound **7** was much lower. It seems that product **7** was rather easily decomposed by the strong base. Ring-closing metathesis (RCM)[16] of compound **7** with the Grubbs' II catalyst in refluxing toluene afforded the bicyclic imide **8** in modest yield (Scheme III), together with the recovered compound **7** (37%). Similar reaction of compound **7** with the Grubbs' I catalyst only gave the recovered starting material.

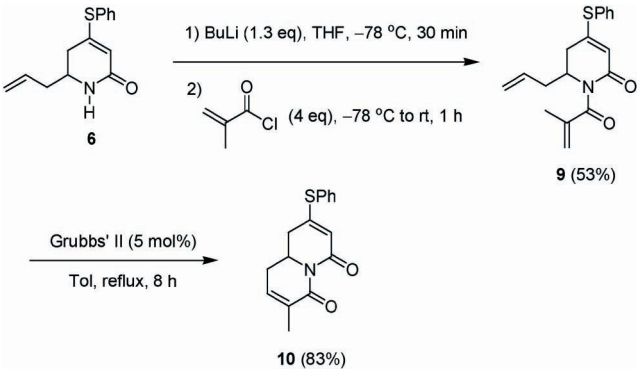
Scheme III Synthesis of bicyclic imide **8**



The conversion of compound **6** to the *N*-acylated product **9** was more successfully carried out by first reacting with BuLi at low temperature, followed by treatment with methacryloyl chloride. The extra methyl group in compound **9** probably made it less susceptible to nucleophilic attack by the strong base. Further RCM reaction of compound **9** with Grubbs' II catalyst provided a good yield of the bicyclic imide **10** (Scheme IV). It was found that both imides **8** and **10** were quite insoluble in ethyl acetate.

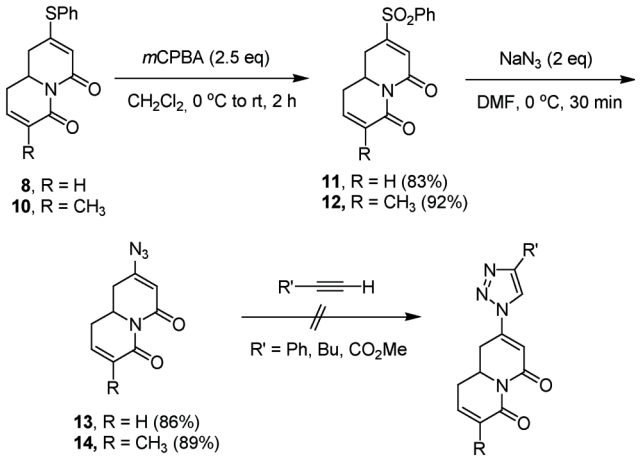
Compounds **8** and **10** were then oxidized with *m*CPBA in CH_2Cl_2 to the corresponding sulfones **11** and **12** in excellent yields. Further treatment of sulfones **11** and **12** with sodium azide in *N*,*N*-dimethylformamide (DMF) at 0 °C afforded the azides **13** and **14** in good yields, respectively (Scheme V). However, we could not successfully react compounds **13** and **14** with terminal alkynes either under thermal reaction conditions[17] or with Cu(I) catalysis at room temperature.[15] One possible reason was that the presumed cycloaddition product was not very soluble in com-

Scheme IV Synthesis of bicyclic imide **10**



mon organic solvents, which made purification of the products rather difficult.

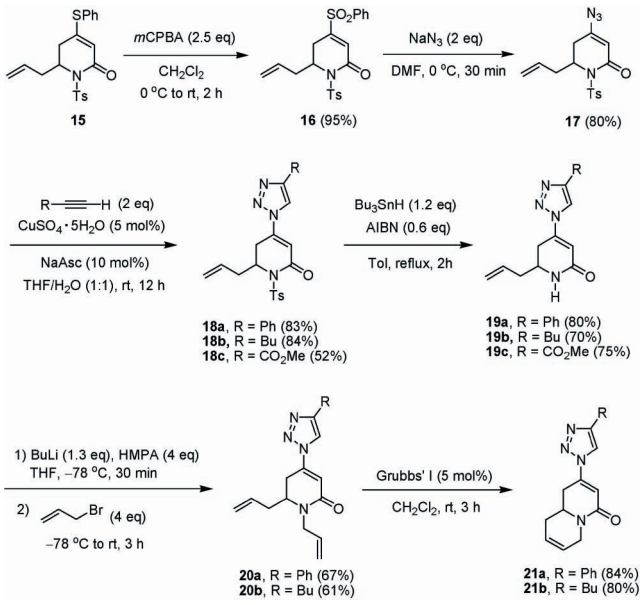
Scheme V Synthesis of azido bicyclic imides **13** and **14**



Having encountered the above difficulties, we then decided to carry out the click chemistry first and then to form the bicyclic imide structure through RCM. Treatment of compound **15**[5a] with *m*CPBA in CH_2Cl_2 provided the sulfone **16** in excellent yield, which was reacted with sodium azide in DMF at 0 °C to give the azide **17** in good yield. Attempted reaction of compound **15** with NaN_3 to give the azide product **17** did not proceed at all. Apparently, the electron-withdrawing sulfonyl group in compound **16** activates its reaction with NaN_3. Further reaction of compound **17** with the terminal alkynes in the presence of cupric sulfate and sodium ascorbate (NaAsc) in THF/H_2O (1:1) at room temperature led to the expected triazole products **18a-c** in fair to good yields. The regiochemistry of compound **18a** was proven by NOESY, which shows that

the proton (δ 8.09) on the triazole ring has significant cross-signals with the H-3 (δ 6.17) of the dihydro-2-pyridone. This result is also in agreement with the literature findings about the regioselective formation of 1,4-disubstituted triazoles.[15] Compounds **18a-c** were treated with Bu_3SnH/AIBN[18] to give the corresponding secondary amides **19a-c** in good yields. Deprotonation of compounds **19a-b** with BuLi at -78 °C in THF in the presence of hexamethylphosphoric amide (HMPA), followed by reaction with allyl bromide provided the *N*-allyl substituted products **20a-b** in fair yields, respectively. However, similar reactions for compound **19c** or the use of other bases (NaH or LDA) did not lead to the expected *N*-allyl product. Apparently, the ester group in compound **19c** was not very stable under these reaction conditions. It was found that the RCM reaction of compounds **20a-b** was successfully carried out in the presence of Grubbs' I catalyst to give the bicyclic imides **21a-b** bearing the triazole structure in good yields, respectively (Scheme VI).

Scheme VI Synthesis of triazolyl-substituted quinolizidine imides



In summary, we have successfully synthesized the triazolyl-substituted quinolizidine imides **21a-b** from the dihydro-2-pyridone **15** in six steps, which include the activation of the 2-pyridone **16** with the phenylsulfonyl group, substitution with sodium azide to give azide **17**, click chemistry to form the triazoles **18**, detosylation with Bu_3SnH/AIBN, *N*-allylation and final RCM reaction. We will study the biological activities of products **21** and the intermediates synthesized.

EXPERIMENTAL

General

Melting points were determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin Elmer 100 series FTIR spectrometer using the ATR (attenuated total reflectance) mode. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or 800 spectrometer operating at 300 or 800, and at 75 or 200 MHz, respectively unless specified otherwise. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN-O-S-Rapid Analyzer or Elementar Vario EL III. Flash column chromatographic purifications were performed using Merck 60 H silica gel.

Acryloyl-6-allyl-4-(phenylthio)-5,6-dihydropyridin-2(1H)-one (7)

To a solution of compound **6** (200 mg, 0.8 mmol) and DMAP (10 mg, 0.08 mmol) in CH_2Cl_2 (4 mL) at room temperature under nitrogen were added sequentially with a syringe Et_3N (0.57 mL, 4 mmol) and acryloyl chloride (0.21 mL, 2.4 mmol). The reaction mixture was refluxed for 24 h, and then the solvent was removed under vacuum. Ethyl acetate (20 mL) was added, and the organic solution was washed with 5% HCl (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:4-1:1) as eluent to give compound **7** (61.9 mg, 51%) as a white solid: mp 73.3-74.1 °C (recryst. CH_2Cl_2); IR (ATR) 3065, 2922, 2853, 1665, 1593, 1389, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55-7.43 (5H, m), 6.98 (1H, dd, *J* = 16.8, 10.5 Hz), 6.35 (1H, dd, *J* = 16.8, 1.8 Hz), 5.83-5.73 (1H, m), 5.70 (1H, dd, *J* = 10.5, 1.8 Hz), 5.27 (1H, d, *J* = 2.4 Hz), 5.14-5.09 (2H, m), 4.86-4.79 (1H, m), 2.82 (1H, ddd, *J* = 17.7, 6.0, 2.4 Hz), 2.50 (1H, dd, *J* = 17.7, 1.5 Hz), 2.46-2.33 (2H, m); ^{13}C NMR ($CDCl_3$) δ 168.4, 163.4, 159.2, 135.5, 133.8, 131.7, 130.5, 130.1, 128.1, 127.7, 118.9, 114.5, 51.3, 36.7, 31.7; EI-MS (relative intensity) *m/z* 299 (M^+, 2), 204 (28), 103 (10), 73 (28), 60 (28), 59 (100), 55 (15); Exact mass calcd for $C_{17}H_{17}NO_2S$ *m/z* 299.0980, EI-HRMS *m/z* 299.0983. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 67.97;

H, 5.70; N, 4.48.

2-(Phenylthio)-9,9a-dihydro-1*H*-quinolizine-4,6-dione (8)

A mixture of compound **7** (125 mg, 0.42 mmol) and Grubbs' II catalyst (17.7 mg, 0.021 mmol) in toluene (10 mL) was refluxed under nitrogen for 4 h. Another portion of Grubbs' II catalyst (17.7 mg, 0.021 mmol) was added, and the reaction mixture was refluxed for 4 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:1) as eluent to give compound **8** (51.7 mg, 57%) as a white solid: mp 123 °C (decomp) (recryst. CH_2Cl_2/hexane); IR (ATR) 3054, 2927, 2853, 1718, 1646, 1604, 1386, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51-7.40 (5H, m), 6.71-6.65 (1H, m), 6.03 (1H, dd, *J* = 9.9, 2.1 Hz), 5.39 (1H, d, *J* = 1.8 Hz), 4.25-4.13 (1H, m), 2.72 (1H, ddd, *J* = 16.8, 12.6, 1.8 Hz), 2.58-2.39 (3H, m); ^{13}C NMR ($CDCl_3$) δ 163.3, 162.5, 155.5, 139.6, 135.3, 130.4, 130.0, 127.1, 126.9, 115.9, 53.5, 35.3, 30.8; EI-MS (relative intensity) *m/z* 271 (M^+, 70), 204 (52), 176 (65), 148 (45), 147 (55), 109 (63), 77 (70), 71 (42), 69 (50), 68 (44), 67 (100), 65 (54), 57 (91), 55 (87), 51 (47); Exact mass calcd for $C_{15}H_{13}NO_2S$ *m/z* 271.0667, EI-HRMS *m/z* 271.0660.

6-Allyl-1-(2-methylacryloyl)-4-(phenylthio)-5,6-dihydropyridin-2(1*H*)-one (9)

To a solution of compound **6** (200 mg, 0.8 mmol) in THF (5 mL) at -78 °C under nitrogen was added slowly with a syringe BuLi (0.42 mL, 2.5 M, 1.04 mmol). After stirring for 30 min, methacryloyl chloride (0.33 mL, 3.2 mmol) was added in one portion. The reaction mixture was slowly warmed to room temperature, and the solvent was removed under vacuum. Ethyl acetate (20 mL) was added, and the organic solution was washed with 5% HCl (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:6-1:1) as eluent to give compound **9** (179.5 mg, 70%) as a white solid: mp 63.2-65.0 °C (recryst. CH_2Cl_2); IR (ATR) 3075, 2923, 1679, 1656, 1591, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55-7.42 (5H, m), 5.85-5.72 (1H, m), 5.35 (1H, d, *J* = 2.4 Hz), 5.16-5.09 (4H, m), 4.63-4.56 (1H, m), 2.84 (1H, ddd, *J* = 17.4, 6.0, 2.4 Hz), 2.55-2.30 (3H, m), 1.95 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.3, 162.9, 159.0, 142.9, 135.4, 133.8, 130.5, 130.0, 127.6, 118.9, 116.4, 114.2, 52.0, 36.6, 31.7, 19.2; EI-MS (relative intensity) *m/z* 313 (M^+, 30), 312 (21), 272 (25), 204 (15), 69 (100), 109 (63), 67 (13); Exact mass calcd for $C_{18}H_{19}NO_2S$ *m/z* 313.1136, EI-HRMS *m/z* 313.1135.

7-Methyl-2-(phenylthio)-9,9a-dihydro-1*H*-quinolizine-4,6-dione (10)

A mixture of compound **9** (250 mg, 0.8 mmol) and Grubbs' II catalyst (33.9 mg, 0.04 mmol) in toluene (16 mL) was refluxed under nitrogen for 8 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:1) as eluent to give compound **10** (188.4 mg, 83%) as a white solid: mp 125 °C (decomp) (recryst. CH_2Cl_2/hexane); IR (ATR) 3044, 2945, 1702, 1609, 1392, 1262 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57-7.42 (5H, m), 6.42 (1H, br s), 5.40 (1H, d, *J* = 2.1 Hz), 4.14-4.07 (1H, m), 2.69 (1H, ddd, *J* = 16.8, 12.3, 2.1 Hz), 2.51-2.37 (3H, m), 1.91 (3H, d, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 164.6, 162.8, 155.3, 135.4, 133.8, 133.6, 130.4, 130.1,127.4, 116.3, 53.6, 35.6, 30.5, 17.2; EI-MS (relative intensity) *m/z* 285 (M^+, 2), 88 (11), 86 (66), 84 (100), 51 (29); Exact mass calcd for $C_{16}H_{15}NO_2S$ *m/z* 285.0823, EI-HRMS *m/z* 285.0820. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.35; H, 5.06; N, 4.90.

General procedure for oxidation with *m*CPBA

To a solution of the sulfide (0.13 mmol) in CH_2Cl_2 (2 mL) in an ice bath was added *m*CPBA (70-75% in H_2O, 0.325 mmol). After 5 min the ice bath was removed, and the mixture was further stirred at room temperature for 2 h. The reaction mixture was then added successively saturated $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (10 mL), and was extracted with CH_2Cl_2 (20 mL). The organic solution was dried over K_2CO_3 and evaporated. The crude product was recrystallized from CH_2Cl_2/hexane to give the purified sulfone products.

2-(Phenylsulfonyl)-9,9a-dihydro-1*H*-quinolizine-4,6-dione (11)

White solid; mp 124 °C (decomp) (recryst. CH_2Cl_2/hexane); IR (ATR) 3070, 2925, 1726, 1664, 1447, 1392, 1264, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92-7.89 (2H, m), 7.77-7.72 (1H, m), 7.69-7.56 (2H, m), 6.77-6.71 (1H, m), 6.68 (1H, d, *J* = 2.7 Hz), 6.03 (1H, dd, *J* = 9.9, 2.4 Hz), 4.27-4.16 (1H, m), 2.85 (1H, dd, *J* = 17.4, 4.5 Hz), 2.63-2.44 (3H, m); ^{13}C NMR ($CDCl_3$) δ 162.7, 161.8, 150.0, 141.0, 136.7, 134.9, 129.9, 128.7, 128.4, 126.3, 54.0, 30.9, 28.8; Exact mass calcd for $C_{15}H_{14}NO_4S$ *m/z* 304.0644 (M^++H), ESI-HRMS *m/z* 304.0644 (M^++H).

7-Methyl-2-(phenylsulfonyl)-9,9a-dihydro-1*H*-quinolizine-4,6-dione (12)

White solid; mp 139 °C (decomp) (recryst. CH_2Cl_2/

hexane); IR (ATR) 3087, 2964, 1717, 1436, 1394, 1287, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92-7.89 (2H, m), 7.77-7.72 (1H, m), 7.65-7.60 (2H, m), 6.68 (1H, d, *J* = 5.7 Hz), 6.49-6.47 (1H, m), 4.20-4.09 (1H, m), 2.84 (1H, dd, *J* = 17.1, 4.2 Hz), 2.50-2.39 (3H, m), 1.90 (3H, d, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 164.1, 162.0, 150.0, 136.7, 135.4, 134.8, 132.9, 129.8, 128.6, 128.5, 53.9, 30.5, 28.9, 17.1; FAB-MS (relative intensity) *m/z* 318 (M^++H, 85), 110 (30), 77 (31), 69 (36), 57 (36), 55 (52), 43 (40), 41 (45), 39 (100); Exact mass calcd for $C_{16}H_{15}NO_4S$ *m/z* 317.0722, FAB-HRMS *m/z* 317.0728.

6-Allyl-4-(phenylsulfonyl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (16)

White solid; mp 163.4-164.6 °C (recryst. CH_2Cl_2/hexane); IR (ATR) 3068, 2926, 1710, 1692, 1639, 1596, 1320, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95-7.87 (4H, m), 7.75-7.70 (1H, m), 7.64-7.59 (2H, m), 7.29 (2H, d, *J* = 8.4 Hz), 6.62 (1H, d, *J* = 2.4 Hz), 5.57-5.43 (1H, m), 4.98 (1H, d, *J* = 10.2 Hz), 4.89-4.82 (1H, m), 4.67 (1H, d, *J* = 17.1 Hz), 2.75-2.66 (2H, m), 2.48-2.42 (4H, m), 2.18-2.10 (1H, m); ^{13}C NMR ($CDCl_3$) δ 160.3, 151.6, 145.5, 136.5, 135.6, 134.9, 131.9, 129.9, 129.5, 129.2, 128.9, 127.0, 120.3, 54.4, 37.9, 26.1, 21.7; Exact mass calcd for $C_{21}H_{22}NO_5S_2$ *m/z* 432.0939 (M^++H), ESI-HRMS *m/z* 432.0945.

General procedure for the reaction of sulfones with sodium azide

To a solution of the sulfone (0.11 mmol) in DMF (1 mL) in an ice bath was added NaN_3 (0.22 mmol). After stirring for 30 min, ethyl acetate (20 mL) was added. The organic solution was washed sequentially with water (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude product was recrystallized from CH_2Cl_2/hexane to give substituted product.

2-Azido-9,9a-dihydro-1*H*-quinolizine-4,6-dione (13)

Orange solid; IR (ATR) 3080, 2963, 2105, 1710, 1640, 1398, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72-6.66 (1H, m), 6.10 (1H, dd, *J* = 9.9, 2.4 Hz), 5.77 (1H, d, *J* = 2.4 Hz), 4.24-4.15 (1H, m), 2.67-2.42 (3H, m), 2.37 (1H, dd, *J* = 17.4, 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 163.7, 163.2, 152.2, 139.5, 127.2, 109.2, 52.9, 33.2, 31.0; Exact mass calcd for $C_9H_8N_4NaO_2$ *m/z* 227.0545 (M^++Na), ESI-HRMS *m/z* 227.0539 (M^++Na).

2-Azido-7-methyl-9,9a-dihydro-1*H*-quinolizine-4,6-dione (14)

Orange solid; IR (ATR) 3001, 2107, 1707, 1637, 1235, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.45-6.42 (1H, m), 5.76 (1H, d, *J* = 2.1 Hz), 4.18-4.11 (1H, m), 2.57 (1H, ddd, *J* = 17.1, 12.3, 2.1 Hz), 2.52-2.38 (2H, m), 2.34 (1H, dd, *J* = 17.1, 4.5 Hz), 1.93 (3H, d, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 164.6, 163.9, 152.2, 133.8 (×2), 109.4, 52.9, 33.3, 30.6, 17.2; Exact mass calcd for $C_{10}H_{10}N_4NaO_2$ *m/z* 241.0701 (M^++Na), ESI-HRMS *m/z* 241.0698 (M^++Na).

6-Allyl-4-azido-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (17)

Orange oil; IR (ATR) 3073, 2109, 1676, 1620, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (2H, d, *J* = 8.4 Hz), 7.31 (2H, d, *J* = 8.4 Hz), 5.82-5.71 (1H, m), 5.52 (1H, d, *J* = 2.3 Hz), 5.19-5.09 (2H, m), 4.90-4.83 (1H, m), 2.82 (1H, ddd, *J* = 17.4, 6.3, 2.3 Hz), 2.63-2.36 (6H, m); ^{13}C NMR ($CDCl_3$) δ 162.1, 153.6, 144.9, 136.6, 133.0, 129.4, 129.1, 119.9, 107.2, 53.4, 38.1, 29.8, 21.7; EI-MS (relative intensity) *m/z* 333 (M^++H, 39), 332 (M^+, 3), 217 (14), 201 (10), 171 (25), 155 (59), 108 (12), 107 (12), 92 (10), 91 (100), 65 (19); Exact mass calcd for $C_{15}H_{16}N_4O_3S$ *m/z* 332.0943, EI-HRMS *m/z* 332.0952.

General procedure for the reaction of azide 17 with alkynes

To a solution of azide **17** (0.28 mmol), $CuSO_4 \cdot 5H_2O$ (0.014 mmol) and NaAsc (0.028 mmol) in THF/H_2O (1:1, 2 mL) was added with a syringe the alkyne (0.56 mmol). The reaction mixture was stirred at room temperature for 12 h, and was evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:4-1:3) and 5% Et_3N as eluent to give purified product.

6-Allyl-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (18a)

White solid; mp 185.0-186.2 °C (recryst. CH_2Cl_2); IR (ATR) 3144, 2924, 2846, 1683, 1647, 1352, 1225, 1162, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.19 (1H, s), 7.98 (2H, d, *J* = 8.4 Hz), 7.89-7.86 (2H, m), 7.48-7.35 (3H, m), 7.30 (2H, d, *J* = 8.4 Hz), 6.22 (1H, d, *J* = 2.6 Hz), 5.87-5.73 (1H, m), 5.17-5.02 (3H, m), 3.76 (1H, dd, *J* = 18.3, 0.9 Hz), 3.24 (1H, ddd, *J* = 18.3, 6.6, 2.6 Hz), 2.65-2.48 (2H, m), 2.48 (3H, s); ^{13}C NMR ($CDCl_3$) δ 162.0, 149.2, 145.7, 145.1, 136.2, 132.5, 129.4, 129.2, 129.08 (×2), 129.02, 126.1, 120.2, 116.8, 108.8, 53.7, 38.4, 28.3, 28.2, 21.7; Exact mass calcd for $C_{23}H_{23}N_4O_3S$ *m/z* 435.1491 (M^++H), ESI-HRMS *m/z* 435.1487 (M^++H).

6-Allyl-4-(4-butyl-1*H*-1,2,3-triazol-1-yl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (18b)

White solid; mp 135.8-136.2 °C (recryst. CH_2Cl_2); IR (ATR) 3129, 2942, 2928, 2871, 1677, 1596, 1341, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (2H, d, *J* = 8.4 Hz), 7.62 (1H, s), 7.33 (2H, d, *J* = 8.4 Hz), 6.07 (1H, d, *J* = 2.6 Hz),

5.87-5.73 (1H, m), 5.17-5.00 (3H, m), 3.73 (1H, dd, *J* = 18.2, 1.2 Hz), 3.20 (1H, ddd, *J* = 18.2, 6.6, 2.6 Hz), 2.75 (2H, t, *J* = 7.5 Hz), 2.66-2.47 (2H, m), 2.44 (3H, s), 1.70-1.63 (3H, m), 1.39 (2H, sextet, *J* = 7.5 Hz), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 162.1, 150.4, 145.9, 145.1, 136.3, 132.6, 129.5, 129.1, 120.2, 118.0, 108.2, 53.7, 38.4, 31.2, 28.3, 25.2, 22.3, 21.7, 13.8; Exact mass calcd for $C_{21}H_{27}N_4O_3S$ *m/z* 415.1804 (M^++H), ESI-HRMS *m/z* 415.1813 (M^++H).

6-Allyl-4-(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (18c)

White solid; mp 196.6-197.8 °C (recryst. CH_2Cl_2); IR (ATR) 3133, 2955, 2923, 2853, 1719, 1677, 1456, 1260, 1167, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, s), 7.99 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 6.29 (1H, d *J* = 2.7 Hz), 5.86-5.72 (1H, m), 5.18-5.03 (3H, m), 3.99 (3H, s), 3.62 (1H, dd, *J* = 18.5, 1.2 Hz), 3.26 (1H, ddd, *J* = 18.5, 6.9, 2.7 Hz), 2.66-2.44 (2H, m), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$) δ 161.3, 160.3, 145.4, 144.9, 141.3, 136.0, 132.4, 129.5, 129.2, 125.0, 120.4, 111.0, 53.5, 52.7, 38.5, 28.4, 21.8; Exact mass calcd for $C_{19}H_{21}N_4O_5S$ *m/z* 417.1233 (M^++H), ESI-HRMS *m/z* 417.1245 (M^++H).

General procedure for removing the tosyl group of compounds 18 with Bu_3SnH/AIBN

To a refluxing solution of the *N*-tosyl compound **18** (0.96 mmol) in degassed toluene (10 mL) was added in one portion a solution of Bu_3SnH (1.15 mmol) and AIBN (0.57 mmol) in tolune (2 mL). The reaction mixture was refluxed for another 2 h. The solvent was then evaporated under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:4-1:1) as eluent to give the secondary amides **19**.

6-Allyl-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2-pyridone (19a)

White solid; mp 160.1-161.5 °C (recryst. CH_2Cl_2/hexane); IR (ATR) 3204, 3193, 3077, 3067, 1669, 1628, 1459, 1439, 1347, 1222, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, s), 7.89-7.87 (2H, m), 7.50-7.39 (3H, m), 6.25 (1H, t, *J* = 1.8 Hz), 5.87 (1H, br s), 5.79-5.74 (1H, m), 5.29-5.23 (2H, m), 3.95-3.84 (1H, m), 3.51 (1H, dd, *J* = 17.5, 5.2 Hz), 2.95 (1H, ddd, *J* = 17.5, 11.4, 1.8 Hz), 2.60-2.51 (1H, m), 2.44-2.34 (1H, m); ^{13}C NMR ($CDCl_3$) δ 166.1, 149.0, 145.3, 132.4, 129.4, 129.1 (×2), 126.1, 120.2, 116.6, 109.2, 49.5, 39.6, 30.3; FAB-MS (relative intensity) *m/z* 281 (M^++H, 100), 253 (45), 179 (45), 177 (45), 150 (100), 126 (58), 124 (84), 68 (33), 67 (33), 62 (44); Exact mass calcd for $C_{16}H_{17}N_4O$ *m/z* 281.1402 (M^++H), FAB-HRMS *m/z* 281.1393.

6-Allyl-4-(4-butyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2-pyridone (19b)

White solid; mp 100.3-101.4 °C (recryst. CH_2Cl_2/hexane); IR (ATR) 3194, 3151, 3071, 2956, 2924, 2855, 1668, 1629, 1441, 1348, 1235, 1041, 861 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, s), 6.14 (2H, br s), 5.87-5.73 (1H, m), 5.27-5.21 (2H, m), 3.91-3.81 (1H, m), 3.46 (1H, *J* = dd, 17.5, 5.1 Hz), 2.90 (1H, ddd, *J* = 17.5, 11.1, 1.5 Hz), 2.77 (2H, t, *J* = 7.5 Hz), 2.57-2.34 (2H, m), 1.69 (2H, quintet, *J* = 7.5 Hz), 1.41 (2H, sextet, *J* = 7.5 Hz), 0.96 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 149.9, 145.5, 132.5, 120.1, 117.9, 108.5, 49.5, 39.6, 31.2, 30.2, 25.2, 22.3, 13.8; FAB-MS (relative intensity) *m/z* 261 (M^++H, 100), 151 (23), 150 (100), 127 (29), 126 (57), 124 (83), 84 (28), 67 (30), 62 (29); Exact mass calcd for $C_{14}H_{21}N_4O$ *m/z* 261.1715 (M^++H), FAB-HRMS *m/z* 261.1717.

6-Allyl-4-(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2-pyridone (19c)

White solid; mp 176.1 °C (decomp) (recryst. CH_2Cl_2/hexane); IR (ATR) 3287, 3147, 2931, 1706, 1627, 1551, 1434, 1343, 1251, 1197, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.51 (1H, s), 6.31 (1H, t, *J* = 1.8 Hz), 5.86-5.72 (2H, m), 5.34-5.20 (2H, m), 4.00 (3H, s), 3.96-3.86 (1H, m), 3.42 (1H, dd, *J* = 17.5, 5.1 Hz), 2.92 (1H, ddd, *J* = 17.5, 11.4, 2.4 Hz), 2.59-2.51 (1H, m), 2.43-2.33 (1H, m); ^{13}C NMR ($CDCl_3$) δ 170.0, 168.7, 149.2, 139.9, 132.8, 119.7, 95.7, 93.3, 51.2, 49.2, 39.6, 33.0; FAB-MS (relative intensity) *m/z* 263 (M^++H, 100), 150 (63), 127 (23), 126 (44), 124 (55), 62 (21), 60 (23), 53 (23); Exact mass calcd for $C_{12}H_{15}N_4O_3$ *m/z* 263.1144 (M^++H), FAB-HRMS *m/z* 263.1139.

General procedure for the *N*-allylation of amides 19

To a solution of compound **19a** (33 mg, 0.12 mmol) and HMPA (82.8 μL, 0.78 mmol) in THF (3 mL) at -78 °C under nitrogen was added dropwise a solution of BuLi (1.6 M in hexane, 95.7 μL, 0.15 mmol). After stirring at -78 °C for 30 min, allyl bromide (40.8 μL, 0.47 mmol) was added in one portion, and the reaction mixture was slowly warmed to room temperature and stirred for another 3 h before it was poured into saturated ammonium chloride solution (15 mL). The solvent was removed by rotary evaporation, and the residue was extracted with ethyl acetate (15 mL × 3), dried ($MgSO_4$), and evaporated under vacuum. The crude product was purified by flash chromatography using ethyl acetate/hexane (1:8-1:1) as eluent to give purified products **20**.

1,6-Diallyl-4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2-pyridone (20a)

White solid; mp 101.8-103.1 °C (recryst. CH_2Cl_2/hexane); IR (ATR) 3102, 2925, 1666, 1621, 1458, 1438, 1225, 1019 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (1H, s), 7.90-7.86 (2H, m), 7.50-7.37 (3H, m), 6.30 (1H, d, *J* = 2.4 Hz), 5.93-5.69 (2H, m), 5.30-5.08 (4H, m), 4.76 (1H, ddd, *J* = 15.6, 3.3, 1.8 Hz), 3.80-3.73 (1H, m), 3.69-3.48 (2H, m), 3.16 (1H, ddd, *J* = 18.0, 6.9, 2.7 Hz), 2.49-2.39 (2H, m); ^{13}C NMR ($CDCl_3$) δ 162.8, 149.0, 142.5, 133.4, 133.2, 129.5, 129.1, 129.0, 126.1, 119.7, 117.8, 116.5, 109.8, 53.6, 47.4, 36.5, 27.8; FAB-MS (relative intensity) *m/z* 321 (M^++H, 7), 59 (72), 53 (70), 52 (100); Exact mass calcd for $C_{19}H_{21}N_4O$ *m/z* 321.1725 (M^++H), FAB-HRMS *m/z* 321.1710.

1,6-Diallyl-4-(4-butyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2-pyridone (20b)

White solid; mp 109-110.7 °C (recryst. CH_2Cl_2/hexane); IR (ATR) 3140, 3100, 2957, 2927, 2857, 1664, 1619, 1444, 1416, 1208, 1001 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (1H, s), 6.16 (1H, d, *J* = 2.7 Hz), 5.91-5.68 (2H, m), 5.30-5.06 (4H, m), 4.78-4.69 (1H, m), 3.76-3.68 (1H, m), 3.58-3.48 (2H, m), 3.10 (1H, ddd, *J* = 18.0, 6.9, 2.7 Hz), 2.76 (2H, t, *J* = 7.5 Hz), 2.46-2.36 (2H, m), 1.74-1.64 (2H, m), 1.41 (2H, sextet, *J* = 7.5 Hz), 0.96 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 163.0, 149.9, 142.7, 133.4, 133.3, 119.6, 117.8, 117.7, 109.1, 53.6, 47.4, 36.4, 31.3, 27.8, 25.3, 22.3, 13.8; FAB-MS (relative intensity) *m/z* 301 (M^++H, 22), 69 (40), 67 (36), 64 (48), 60 (52), 59 (39), 58 (38), 54 (79), 53 (100); Exact mass calcd for $C_{17}H_{25}N_4O$ *m/z* 301.2011 (M^++H), FAB-HRMS *m/z* 301.2028.

General procedure for the RCM reaction of compounds 20

A mixture of compound **20b** (98.6 mg, 0.328 mmol) and Grubbs' I catalyst (13.5 mg, 0.016 mmol) in CH_2Cl_2 (4 mL) was stirred under nitrogen at room temperature for 3 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography using ethyl acetate/hexane (1:4) and 5% Et_3N as eluent to give products **21**.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-9,9a-dihydro-1*H*-4(6*H*)-quinolizinone (21a)

White solid; mp 225.5-227.1 °C (recryst. CH_2Cl_2/hexane); IR (ATR) 3104, 3029, 1677, 1662, 1617, 1443, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (1H, s), 7.90-7.86 (2H, m), 7.51-7.38 (3H, m), 6.26 (1H, t, *J* = 1.5 Hz), 5.88-5.77 (2H, m), 4.70 (1H, br d, *J* = 18.7 Hz), 4.04 (1H, ddt, *J* = 11.1, 4.2, 6.9), 3.71 (1H, br d, *J* = 18.7 Hz), 3.56 (1H, ddd, *J* = 18.0, 7.2, 1.2 Hz), 3.22 (1H, ddd, *J* = 18.0, 6.3, 0.6 Hz), 2.55-2.44 (1H, m), 2.32-2.21 (1H, m); ^{13}C NMR ($CDCl_3$) δ 163.9, 149.0, 142.5, 129.5, 129.12, 129.07, 126.2, 124.9, 124.2, 116.3, 109.3, 50.9, 42.9, 31.7, 29.6; FAB-MS (relative intensity) *m/z* 293 (M^++H, 57), 265 (40), 152 (24), 150 (100), 127 (27), 125 (54), 124 (81), 84 (26), 67 (33), 62 (32); Exact mass calcd for $C_{17}H_{17}N_4O$ *m/z* 293.1402 (M^++H), FAB-HRMS *m/z* 293.1395.

2-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-9,9a-dihydro-1*H*-4(6*H*)-quinolizinone (21b)

White solid; mp 139.8 °C (decomp) (recryst. CH_2Cl_2/hexane); IR (ATR) 3140, 2956, 1678, 1664, 1622, 1563, 1423, 1332, 1209, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (1H, s), 6.14 (1H, t, *J* = 1.2 Hz), 5.86-5.75 (2H, m), 4.67 (1H, br d, *J* = 18.4 Hz), 3.99 (1H, ddt, *J* = 11.1, 4.5, 6.6 Hz), 3.69 (1H, br d, *J* = 18.4 Hz), 3.50 (1H, ddd, *J* = 18.0, 7.2, 1.2 Hz), 3.17 (1H, dd, *J* = 18.0, 6.0 Hz), 2.77 (2H, t, *J* = 7.6 Hz), 2.52-2.41 (1H, m), 2.26-2.18 (1H, m), 1.74-1.64 (2H, m), 1.41 (2H, sextet, *J* = 7.2 Hz), 0.95 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 164.1, 149.9, 142.6, 124.9, 124.2, 117.7, 108.6, 50.8, 42.8, 31.6, 31.3, 29.5, 25.3, 22.3, 13.8; FAB-MS (relative intensity) *m/z* 273 (M^++H, 100), 245 (55), 150 (28), 124 (27); Exact mass calcd for $C_{15}H_{21}N_4O$ *m/z* 273.1715 (M^++H), FAB-HRMS *m/z* 273.1704.

ACKNOWLEDGEMENTS

Financial support of this work by the National Science Council of the Republic of China is gratefully acknowledged (NSC 97-2113-M-030-MY3).

REFERENCES

1. (a) Rubiralta, M.; Giralt, E.; Diez, E. *Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*, Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 43, p 185. (c) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637. (d) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
2. (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
3. (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: Orlando, 1987. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (c) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (d) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (e) Rowland, G. B.; Rowland, E. B.; Zhang, Q.; Antilla, J. C. *Curr. Org. Chem.* **2006**, *10*, 981.

4. (a) Chou, S. S. P.; Hung, C. C. *Tetrahedron Lett*. **2000**, *41*, 8323. (b) Chou, S. S. P.; Hung, C. C. *Synthesis* **2001**, 2450.
5. (a) Chou, S. S. P.; Chiu, H. C.; Hung, C. C. *Tetrahedron Lett*. **2003**, *44*, 4653. (b) Chou, S. S. P.; Ho, C. W. *Tetrahedron Lett*. **2005**, *46*, 8551. (c) Chou, S. S. P.; Hsieh, H. I.; Hung, C. C. *J. Chin. Chem. Soc.* **2006**, *53*, 891. (d) Chou, S. S. P.; Liang, C. F.; Lee, T. M.; Liu, C. F. *Tetrahedron* **2007**, *63*, 8267. (e) Chou, S. S. P.; Chen, P. W. *Tetrahedron* **2008**, *64*, 1879. (f) Chou, S. S. P.; Wang, H. C.; Chen, P. W.; Yang, C. H. *Tetrahedron* **2008**, *64*, 5291. (g) Chou, S. S. P.; Liu, C. F. *J. Chin. Chem. Soc.* **2010**, *57*, 811. (h) Chou, S. S. P.; Cai, Y. L. *Tetrahedron* **2011**, *67*, 1183. (i) Chou, S. S. P.; Chung, Y. C.; Chen, P. A.; Chiang, S. L.; Wu, C. J. *J. Org. Chem.* **2011**, *76*, 692. (j) Chou, S. S. P.; Yang, T. H.; Wu, W. S.; Chiu, T. H. *Synthesis* **2011**, 759. (k) Chou, S. S. P.; Huang, C. W.; Chang, C. C. *Tetrahedron* **2011**, *67*, 4505. (l) Chou, S. S. P.; Lee, B. H.; Ni, C. H.; Lin, Y. C. *Tetrahedron* **2011**, *67*, 5395.
6. (a) Wang, S.-J.; Chou, S.-H.; Kuo, Y.-C.; Chou, S. S. P.; Zeng, W.-F.; Leu, J.-Y.; Huang, R.-F. S.; Liew, Y.-F. *Acta Pharmacol. Sin*. **2008**, *29*, 1289. (b) Chou, S.-H.; Chou, S. S. P.; Liew, Y.-F.; Leu, J.-Y.; Wang, S.-J.; Huang, R.-F. S.; Tzeng, W.-F.; Kuo, Y.-C. *Molecules* **2009**, *14*, 2345. (c) Liew, Y.-F.; Huang, C.-T.; Chou, S. S. P.; Kuo, Y.-C.; Chou, S.-H.; Leu, J.-Y.; Tzeng, W.-F.; Wang, S.-J.; Tang, M.-C.; Huang, R.-F. S. *Molecules* **2010**, *15*, 1632.
7. Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K. D.; Tong, W. P.; Huang, X. Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326.
8. (a) Shoji, A.; Kuwahara, M.; Ozaki, H.; Sawai, H. *J. Am. Chem. Soc.* **2007**, *129*, 1456. (b) Luzzio, F. A.; Duveau, D. Y.; Lepper, E. R.; Figg, W. D. *J. Org. Chem.* **2005**, *70*, 10117. (c) Franks, M. E.; Macpherson, G. R.; Figg, W. D. *Lancet* **2004**, *363*, 1802.
9. Nakano, T.; Djerassi, C.; Corral, R. A.; Orazi, O. O. *J. Org. Chem.* **1961**, *26*, 1184.
10. Butler, D. E.; Leonard, J. D.; Caprathe, B. W.; L'Italien, Y. J.; Pavia, M. R.; Hershenson, F. M.; Poschel, P. H.; Marriott, J. G. *J. Med. Chem.* **1987**, *30*, 498.
11. Pavia, M. R.; Moos, W. H.; Hershenso, F. M. *J. Org. Chem.* **1990**, *55*, 560.
12. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
13. (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev.* **2010**, *39*, 1252. (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (d) Bakunov, S. A.; Bakunova, S. M.; Wenzler, T.; Ghebru, M.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. *J. Med. Chem.* **2010**, *53*, 254.
14. (a) van Steenis, D. J. V. C.; David, O. R. P.; van Strijdonck, G. P. F.; van Maarseveen, J. H.; Reek, J. N. H. *Chem. Commun.* **2005**, 4333. (b) He, Y.; Bian, Z.; Kang, C.; Cheng, Y.; Gao, L. *Chem. Commun.* **2010**, 3532. (c) Goldup, S. M.; Leigh, D. A.; McGonigal, P. R.; Ronaldson, V. E.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2010**, *132*, 315. (d) Ornelas, C.; Broichhagen, J.; Weck, M. *J. Am. Chem. Soc.* **2010**, *132*, 3923.
15. (a) Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin,V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
16. (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
17. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; p 1.
18. Parsons, A. F.; Pettifer, R. M. *Tetrahedron Lett.* **1996**, *37*, 1667.

