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CYCLOADDITION REACTIONS OF 1-AZADIENES DERIVED FROM HYDRAZONES WITH ELECTRON-DEFICIENT DIENOPHILES[#]

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Abstract – The aza-Diels–Alder reaction of 1-aza-1,3-butadienes derived from hydrazones, with electron-deficient dienophiles is reported. When there is not substitution at C-2 in the starting 1-azadiene, fused-pyridine derivatives are obtained. However, the use of 1-azadienes substituted with a methyl group at C-2 gave the corresponding pyridazinone derivative.

INTRODUCTION

Hydrazones constitute an important class of compounds due to the rich chemistry of the hydrazono group and have attracted a great deal of attention in recent years because of their range of applications.[1] They have been extensively used as versatile precursors in acyclic[2] and heterocyclic synthesis,[3] and also form part of the structure of new azapeptides,[4] as well as biologically active compounds.[5]

Azabutadienes have proved to be efficient heterodienes in aza-Diels–Alder processes,[6,7] and unsaturated hydrazones have been shown to be a versatile tool for the construction of six-membered heterocycles by means of the Diels-Alder reactivity of these substrates as 1-azadienes[8] (**I**, $R^1 = NMe_2$) (Figure 1).

In this context, we have been involved in the synthesis of 1-aza- (**I**),[9] 2-aza-(**II**),[10] and 1,2-diaza-1,3-butadienes (**III**)[11] as well as new strategies for the preparation of nitrogen heterocyclic compounds.[12] As a continuation of our work in the chemistry of new substituted nitrogen heterocycles, here we aim to explore the behaviour of 1-azadienes derived from hydrazones (**I**, $R^1 = NMe_2$) towards electron-deficient dienophiles such as *N*-phenylmaleimide and bromomaleic anhydride, as well as the effect of subtituents at C-2 position of the azadiene. This strategy could open new entries for the preparation of substituted six-membered heterocycles.

[#] Dedicated to Prof. Barry M. Trost on the occasion of his 65th Birthday.

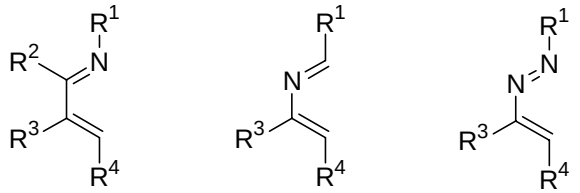
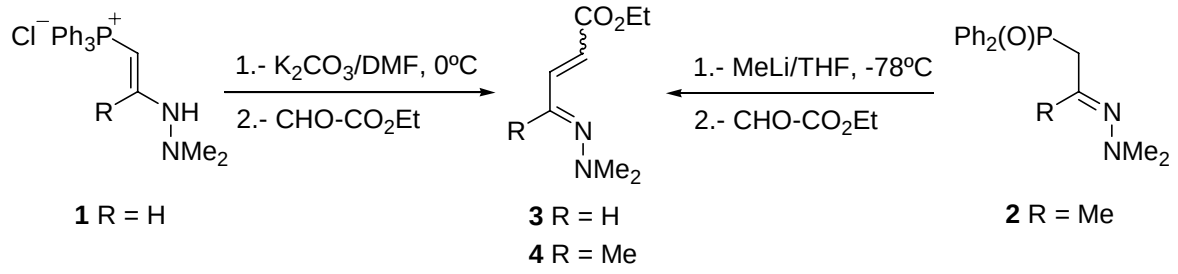


Figure 1. 1-(**I**), 2-azadienes (**II**), and 1,2-diazadienes (**III**).

RESULTS AND DISCUSSION

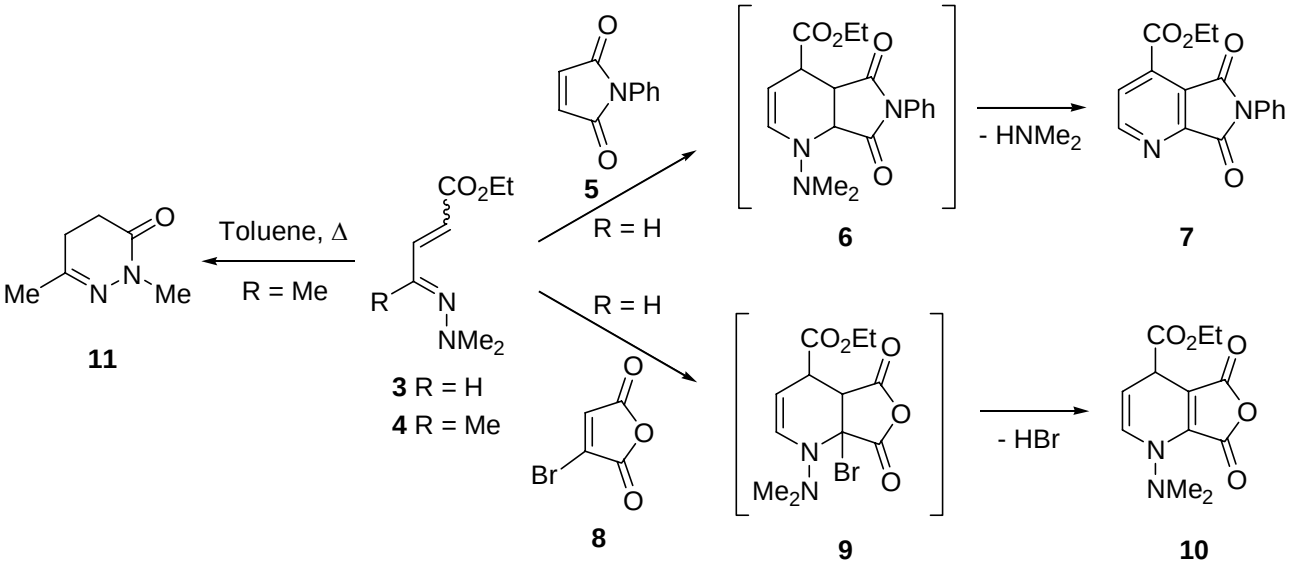
1-Azadienes (**3**) and (**4**) derived from hydrazones were easily prepared by homologation of functionalized hydrazones (**1**) and (**2**) into their vinylogous compounds (Scheme 1). Thus, β-enehydrazinophosphonium salt (**1**) (R = H), synthesized according to the Cristau procedure,[13] was treated with a weak base such as potassium carbonate in DMF followed by Wittig reaction of the generated phosphorane with ethyl glyoxalate leading to 1-azadiene (**3**) (R = H) as a mixture of *E*- and *Z*-configurations for the carbon-carbon double bond (Scheme 1). In the same way, metalation of β-hydrazonophosphine oxides (**2**) (R = Me)[9b] with methyllithium followed by addition of ethyl glyoxalate led exclusively to the formation of (*E*)-α,β-unsaturated hydrazone (**4**) (R = Me) substituted with a methyl group at C-2 position (Scheme 1) in a stereoselective fashion. Compounds (**3**) and (**4**) were characterized based on their NMR spectrocopic data and MS spectrometry (see EXPERIMENTAL). Vicinal coupling constant ($^3J_{HH}$) of 15.4 and 16.2 Hz between the vinylic protons of compounds (**3**) and (**4**) are consistent with the *E*-configuration of the carbon-carbon double bond.



Scheme 1.

Next, the behavior of 1-azadiene (**3**) (R = H) (Scheme 2) as heterodiene with electron-poor dienophiles was explored. Thus, when azadiene (**3**) was treated with *N*-phenylmaleimide (**5**) in refluxing xylene for 3 days, fused-pyridine (**7**) was obtained in low yield with several unrecognizable compounds. The formation of this pyridine (**7**) could be explained through a initial [4+2] cycloaddition reaction of 1-azadiene (**3**) with *N*-phenylmaleimide (**5**) as dienophile to give tetrahydropyridine (**6**), which

aromatization with the loss of dimethylamine afforded substituted pyridine (**7**) (Scheme 2). Analogously, 1-azadiene (**3**) (R = H) react with two equivalents of bromomaleic anhydride (**8**) in chloroform at room temperature to give dihydropyridine (**10**) in almost quantitative yield (Scheme 2). The use of halogenated dienophiles allow us to fix the regiochemistry of the tetrahydropyridine (**9**) obtained as intermediate of the [4+2] cycloaddition reaction of 1-azadiene (**3**) with bromomaleic anhydride (**8**), in a similar way to that previously reported by haloquinones[14a] and halonaphthoquinones.[14b,c] β-Elimination of bromhydric acid in intermediate (**9**) afforded dihydropyridine (**10**).



Scheme 2.

Different behavior was observed when 2-methyl-substituted 1-azadiene (**4**) (R = Me) reacted with electron-poor dienophiles such as *N*-phenylmaleimide, or electron-rich dienophiles such as ethyl vinyl ether. In all cases, the formation of cycloadducts was not observed and starting materials were recovered. However, heating 1-azadiene (**4**) (R = Me) in refluxing toluene led to the formation of pyridazinone (**11**) (Scheme 2). Pyridazinones are important heterocycles in medicinal chemistry.[15] As reported by other authors,[16] the presence of a methyl group at C-2 of the 1-azadiene system (**4**) shifts the dimethylamino group at N-1 out of the plane (steric inhibition of conjugation), deactivating the diene system and hindering the cycloaddition reaction with dienophiles.

In summary, 1-aza-1,3-butadienes (**3**) and (**4**) derived from hydrazones and substituted with a carboxylic group at C-4 have been reported. These azadienes are a class of heterodienes of great interest, owing to their aza-Diels–Alder reactivity for the preparation of substituted dihydropyridines and pyridines. Electron-deficient dienophiles such as *N*-phenylmaleimide and bromomaleic anhydride react with C-2 unsubstituted 1-azadienes to afford pyridine (**7**) and dihydropyridine (**10**) derivatives, respectively.

However, 1-azadienes substituted with a methyl group at C-2 of the azadiene system do not react with electron-poor or electron-rich dienophiles, and only the corresponding pyridazinone derivative (**11**) has been isolated. Through the strategies reported in this paper new access to polysusbstituted nitrogen containing heterocycles can be designed.

EXPERIMENTAL

General. Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC's were performed with silica gel 60 F_{254} plates. Spot visualization was accomplished by UV light or $KMnO_4$ solution. Flash chromatography was carried out using silica gel 60 (230–400 mesh). Melting points were determined with an Electrothermal IA9100 digital apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Unity Plus 300 MHz spectrometer, using tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.24 ppm) for ^{1}H NMR spectra and chloroform (77.0 ppm) for ^{13}C NMR spectra. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet) or m (multiplet). Coupling constants (*J*) are reported in Hertz. Low-resolution MS spectra were obtained on a Hewlett Packard 5971 MSD Series spectrometer at 50–70 eV by electron impact (EI). Data are reported in the form *m/z* (intensity relative to base peak = 100). IR spectra were taken on a Nicolet FTIR Magna 550 spectrophotometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1}. Elemental analyses were performed in a Perkin Elmer Model 240 instrument. Enehydrazine derived from phosphonium salts (**1**) (R = H)[15] and β-hydrazono phosphine oxide (**2**) (R = Me)[11b] were synthesized according to literature procedures.

Preparation of *Z*- and *E*-4-dimethylhydrazonobut-2-enoic acid ethyl ester (3). To a stirred solution of phosphonium salt (**1**) (1.91 g, 5 mmol) in DMF (25 mL), potassium carbonate (1.38 g, 10 mmol) was added dropwise under a nitrogen atmosphere and at 0 ºC. After 15 min at the same temperature, a solution of ethyl glyoxalate (0.61 g, 6 mmol) in DMF (5 mL) was added, and the reaction was kept to reach room temperature for 1 h. The crude mixture was then extracted with Et_2O (2 x 15 mL), and washed with a saturated solution of ammonium chloride (2 x 10 mL). The solvent was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash-chromatography (silica gel, AcOEt/hexanes 3:7) to give **3** (0.52 g, 62%) as a pale yellow oil. Data for **3**: (*Rf* = 0.93, AcOEt/hexanes 1:1). ^{1}H NMR ($CDCl_3$) δ 1.19-1.25 (m, 3H, *Z* and *E*), 2.97 and 3.00 (s, 6H, *E* and *Z*), 4.09-4.16 (m, 2H, *E* and *Z*), 5.53 (d, $^3J_{HH}$ = 11.3 Hz, 1H, *Z*), 5.76 (d, $^3J_{HH}$ = 15.4 Hz, 1H, *E*), 5.53 (d, $^3J_{HH}$ = 11.3 Hz, 1H, *Z*), 6.62-6.65 (m, 1H, *Z*), 6.81 (d, $^3J_{HH}$ = 9.3 Hz, 1H, *E*), 7.34 (dd, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 15.4 Hz, 1H, *E*), 7.95

(d, $^3J_{HH}$ = 9.4 Hz, 1H, *Z*); ^{13}C NMR ($CDCl_3$) δ (*E*-isomer) 14.2, 42.2, 59.8, 117.4, 128.4, 143.2, 167.2; (*Z*-isomer) 14.2, 42.2, 59.5, 112.7, 129.1, 143.5, 167.2; IR (NaCl) 2985, 2892, 1706, 1613, 1540, 1374, 1255; MS (EI) m/z 170 (M^+, 68). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found C, 56.63; H, 8.30; N, 16.41.

Synthesis of *E*-4-dimethylhydrazonopent-2-enoic acid ethyl ester (4). To a -78 ºC solution of β-hydrazonophosphine oxide (**2**) (1.50 g, 5 mmol) in THF (100 mL), a 1.6 M solution of MeLi (3.4 mL, 6 mmol) in THF (5 mL) was added dropwise under a nitrogen atmosphere. After 1 h stirring at the same temperature, a solution of ethyl glyoxalate (0.61 g, 6 mmol) in THF (5 mL) was added, and the reaction was kept to reach rt for 2 h. The crude mixture was then evaporated under vacuum, diluted with CH_2Cl_2 (25 mL), washed with water (3 x 15 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash-chromatography (silica gel, AcOEt/hexanes 1:9) to give **4** (0.66 g, 72%) as a pale yellow oil. Data for **4**: (*Rf* = 0.21, Et_2O/hexanes 1:10). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.06 (s, 3H), 2.67 (s, 6H), 4.22 (t, $^3J_{HH}$ = 7.2 Hz), 6.13 (d, $^3J_{HH}$ = 16.2 Hz, 1H), 7.30 (d, $^3J_{HH}$ = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.8, 46.6, 60.2, 121.0, 145.2, 155.9, 165.7; IR (NaCl) 2960, 2868, 1723, 1637, 1473, 1262; MS (EI) m/z 184 (M^+, 23). Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found C, 58.56; H, 8.74; N, 15.23.

Synthesis of 5,7-dioxo-6-phenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-4-carboxylic acid ethyl ester (7). To a stirred solution of 1-azadiene (**3**) (0.17 g, 1 mmol) in xylene (10 mL) was added *N*-phenylmaleimide (0.35 g, 2 mmol) under a nitrogen atmosphere. The mixture was stirred and refluxed for 72 h. The solvent was evaporated under vacuum and the crude product was purified by flash-chromatography (silica gel, AcOEt/hexanes 1:9) and crystallized from a mixture of CH_2Cl_2/pentane (1:2) to give **7** (0.086 g, 29%) as a white solid. Data for **7**: mp 106-107 ºC. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 4.47 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 7.39-7.50 (m, 5H), 7.83 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 9.09 (d, $^3J_{HH}$ = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 63.1, 126.5, 126.6, 128.7, 129.3, 130.9, 137.8, 152.0, 156.1, 162.8, 163.6; IR (KBr) 3436, 2919, 1739, 1374; MS (EI) m/z 296 (M^+, 100). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found C, 64.79; H, 4.12; N, 9.50.

Synthesis of 1-dimethylamino-5,7-dioxo-1,4,5,7-tetrahydrofuro[3,4-*b*]pyridine-4-carboxylic acid ethyl ester (10). To a stirred solution of 1-azadiene (**3**) (0.17 g, 1 mmol) in THF (5 mL), bromomaleic anhydride (0.27 g, 1.5 mmol) and sodium bicarbonate (0.17 g, 2 mmol) was added under a nitrogen atmosphere. The mixture was stirred at rt for 36 h. The solvent was evaporated under vacuum and the crude product was diluted in CH_2Cl_2. The salts, thus formed, were filtered and the solvent was evaporated under vacuum. The crude product was purified by flash-chromatography (silica gel, AcOEt/hexanes 1:9)

to give **10** (0.26 g, 98%) as a pale yellow oil. Data for **10**: (*Rf* = 0.62, AcOEt/hexanes 1:1). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.66 (s, 6H), 4.11-4.23 (m, 3H), 5.11 (dd, $^3J_{HH}$ = 4.1 Hz, $^3J_{HH}$ = 8.2 Hz, 1H), 6.36 (d, $^3J_{HH}$ = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 37.3, 44.4, 61.8, 105.0, 126.4, 141.6, 143.2, 157.6, 162.7, 169.7; IR (NaCl) 3317, 2985, 2939, 1759, 1248; MS (EI) m/z 266 (M^+, 3). Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found C, 54.27; H, 5.28; N, 10.47.

Synthesis of 2,6-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (11). A solution of 1-azadiene (**4**) (0.18 g, 1 mmol) in toluene (5 mL) was refluxed under a nitrogen atmosphere for 3 days. The solvent was evaporated under vacuum and the crude product was purified by flash-chromatography (silica gel, AcOEt) to give **11** (0.032 g, 25%) as a pale yellow oil. Data for **11**: (*Rf* = 0.21, AcOEt/hexanes 1:1). ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.38-2.40 (m, 4H), 3.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.9, 26.4, 36.0, 153.1, 165.2; IR (NaCl) 3356, 2912, 1745, 1222; MS (EI) m/z 126 (M^+, 100). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21. Found C, 56.96; H, 8.02; N, 22.23.

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REFERENCES

1. For reviews see: (a) M. C. Elliot, 'Comprehensive Organic Functional Group Transformations II,' Vol. 3, ed. by A. R. Katritzky and R. J. K. Taylor, Elsevier, Oxford, 2005, p. 469. (b) T. Vilaivan, W. Bhanthumnavin, and Y. Sritana-Anant, *Curr. Org. Chem.,* 2005, **9**, 1315. (c) B. A. Murray, *Org. React. Mech.,* 2003, 1-33. (d) A. Job, C. F. Carsten, W. Bettaray, and D. Enders, *Tetrahedron,* 2002, **58**, 2253. (e) D. E. Bergbreiter and M. Momongan, 'Comprehensive Organic Synthesis,' Vol. 2, ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 503.
2. For recent contributions see: (a) G. R. Cook, R. Kargbo, and B. Maity, *Org. Lett.,* 2005, **7**, 2767. (b) D. Enders and M. Backes, *Tetrahedron: Asymmetry,* 2004, **15**, 1813. (c) C. Ogawa, M. Sugiura, and S. Kobayashi, *Angew. Chem., Int. Ed.,* 2004, **43**, 6491.
3. For recent contributions see: (a) M. Ciesielski, D. Pufky, and M. Doering, *Tetrahedron,* 2005, **61**, 5942. (b) I. Fernández, V. Valdivia, B. Gori, F. Alcudia, E. Alvarez, and N. Khiar, *Org. Lett.,* 2005, **7**, 1307. (c) D. H. Reza, K. Aghapoor, and M. Tajbakhsh, *Tetrahedron Lett.,* 2004, **45**, 4167. (d) L. Patient, M. B. Berry, S. J. Coles, M. B. Hursthouse, and J. D. Kilburn, *Chem. Commun.,* 2003, 2552.

4. (a) R. E. Melendez and W. D. Lubell, *J. Am. Chem. Soc*., 2004, **126**, 6759. (b) W. P. Malachowski, C. Tie, K. Wang, and R. L. Broadrup, *J. Org. Chem.,* 2002, **67**, 8962.
5. (a) R. Maccari, R. Ottana, and M. G. Vigorita, *Bioorg. Med. Chem. Lett*., 2005, **15**, 2509. (b) J. Easmon, G. Heinisch, G. Pürstinger, T. Langer, and J. K. Österreicher, *J. Med. Chem.,* 1997, **40**, 4420. (c) M. A. Avery, S. Mehrotra, J. D. Bonk, J. A. Vroman, D. K. Goins, and R. Miller, *J. Med. Chem*., 1996, **39**, 2900. (d) H. Maehr, C. M. Liu, N. J. Pelleroni, T. Smallheer, L. Todaso, T. H. Williams, and J. F. Blount, *J. Antibiotics*, 1986, **39**, 17.
6. For reviews see: (a) E. M. Stocking and R. M. Williams, *Angew. Chem., Int. Ed.*, 2003, **42**, 3078. (b) K. C. Nicolau, S. A. Snyder, T. Montagnon, and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1669. (c) S. Jayakumars, M. P. S. Ishar, and M. P. Mahajan, *Tetrahedron*, 2002, **58**, 379. (d) P. Buonora, J. C. Olsen, and T. Oh, *Tetrahedron*, 2001, **57**, 6099. (e) L. Ghosez, 'Stereocontrolled Organic Synthesis,' Backwell, Oxford, 1994, pp. 193-233.
7. For recent contributions see: (a) K. C. Nicolau, B. S. Safina, M. Zak, S. H. Lee, M. Nevalainen, M. Bella, A. A. Estrada, C. Funke, F. J. Zecri, and S. Bulat, *J. Am. Chem Soc.*, 2005, **127**, 11159. (b) M. Altuna-Urquijo, S. P. Stanforth, and B. Tarbit, *Tetrahedron Lett.*, 2005, **46**, 6111. (c) K. C. Nicolau, M. Nevalainen, B. S. Safina, M. Zak, and S. Bulat, *Angew. Chem., Int. Ed*., 2002, **41**, 1941.
8. (a) F. Pautet, P. Nebois, Z. Bouariz, and H. Fillion, *Heterocycles*, 2001, **54**, 2509. (b) M. Behhorouz and M. Ahmadian, *Tetrahedron*, 2000, **56**, 5259. (c) D. L. Boger, 'Comprehensive Organic Synthesis,' Vol. 5, ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 451. (d) L. Ghosez, B. Serckx-Poncin, M. Rivera, P. Bayard, F. Sainte, A. Demoulin, A. M. Hesbain-Frisque, A. Mockel, L. Muñoz, and C. Bernard-Henriet, *Lectures Heterocyclic Chem.*, 1985, **8**, 69.
9. (a) F. Palacios, D. Aparicio, J. M. de los Santos, and E. Rodríguez, *Tetrahedron*, 1998, **54**, 599. (b) F. Palacios, D. Aparicio, and J. M. de los Santos, *Tetrahedron*, 1994, **50**, 12727.
10. (a) F. Palacios, E. Herrán, and G. Rubiales, *J. Org. Chem.*, 2002, **67**, 2131. (b) F. Palacios, C. Alonso, P. Amezua, and G. Rubiales, *J. Org. Chem.*, 2002, **67**, 1941. (c) F. Palacios, E. Herrán, and G. Rubiales, *J. Org. Chem.*, 1999, **64**, 6239. (d) F. Palacios, C. Alonso, and G. Rubiales, *J. Org. Chem.*, 1997, **62**, 1146.
11. (a) F. Palacios, D. Aparicio, Y. López, and J. M. de los Santos, *Tetrahedron*, 2005, **61**, 2815. (b) F. Palacios, D. Aparicio, Y. López, J. M. de los Santos, and C. Alonso, *Eur. J. Org. Chem.*, 2005, 1142. (c) F. Palacios, D. Aparicio, and J. M. de los Santos, *Tetrahedron*, 1999, **55**, 13767.
12. For contributions see: (a) F. Palacios, C. Alonso, M. Rodríguez, E, Martínez de Marigorta, and G. Rubiales, *Eur. J. Org. Chem.*, 2005, 1795. (b) F. Palacios, C. Alonso, G. Rubiales, and M. Villegas, *Tetrahedron*, 2005, **61**, 2779. (c) F. Palacios, C. Alonso, C. Tobillas, and G. Rubiales, *Heterocycles*,

2004, **64**, 229. (d) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, and J. M. Alonso, *Tetrahedron*, 2004, **60**, 8937. (e) F. Palacios, D. Aparicio, A. M. Ochoa de Retana, J. M. de los Santos, J. I. Gil, and J. M. Alonso, *J. Org. Chem.*, 2002, **67**, 7283. (f) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, and R. López de Munain, *Org. Lett.*, 2002, **4**, 2405.

13. H. J. Cristau and M. B. Gasc, *Tetrahedron Lett*., 1990, **31**, 341.
14. (a) J. M. Pérez, P. López-Alvarado, C. Avendaño, and J. C. Meléndez, *Tetrahedron Lett.*, 1998, **39**, 673. (b) Y. Kitahara, F. Tamura, and A. Kubo, *Tetrahedron Lett.*, 1997, **38**, 4441. (c) L. Chaker, F. Pautet, and H. Fillion, *Heterocycles*, 1995, **41**, 1169.
15. (a) F. Ujjainwalla, D. Warner, C. Snedden, R. D. Grisson, T. F. Walsh, M. J. Wyvratt, R. N. Kalyani, T. McNeil, R. Tang, D. H. Weinberg, L. Van der Ploeg, and M. T. Goulet, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4023. (b) A. Coelho and E. Sotelo, *J. Comb. Chem.*, 2005, **7**, 526. (c) S.-G. Lee, J.-J. Kim, H.-K. Kim, D.-H. Kweon, Y.-J. Kang, S.-D. Cho, S.-K. Kim, and Y.-J. Yoon, *Curr. Org. Chem.*, 2004, **8**, 1463. (d) F. Manetti, F. Corelli, G. Strappaghetti, and M. Botta, *Curr. Med. Chem.*, 2002, **9**, 1303.
16. R. Tamion, C. Mineur, and L. Ghosez, *Tetrahedron Lett.*, 1995, **36**, 8977.