ORGANIC LETTERS

2003
Vol. 5, No. 9
1511−1514

# Alkenyl C–H Insertion of Iodonium Ylides into Pyrroles: Studies toward the Total Syntheses of Tolmetin and Amtolmetin Guacil

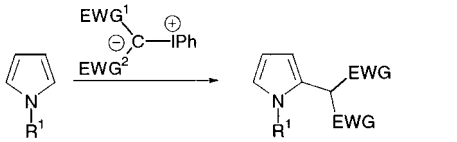
**Christina Batsila, Efstathios P. Gogonas, George Kostakis, and Lazaros P. Hadjiarapoglou***

*Section of Organic Chemistry and Biochemistry, Department of Chemistry, University of Ioannina, GR-45110 Ioannina, Greece*

*lxatziar@cc.uoi.gr*

**Received February 20, 2003**

## ABSTRACT




**The thermal-catalyzed or photochemical reaction of iodonium ylides with pyrroles yields exclusively α-substituted pyrroles in moderate to good yields.**

The transition-metal-catalyzed decomposition of diazo compounds has tremendous potential[1] in organic synthesis. The in situ formation of metallo carbenoids and the transfer of the carbene moiety into a suitable acceptor has found widespread application in the total synthesis of natural products. But this methodology suffers since diazo compounds are considered to be potentially explosive, toxic, and carcinogenic compounds.

Alternatively, iodonium ylides[2] have been recognized as synthetic equivalents of the corresponding diazo compounds, without major drawbacks except that an active methylene compound is required for their facile preparation.[3] The photochemical or Cu-catalyzed decomposition[4] of these stable iodonium ylides affords products typically of carbene (or carbenoids) reactions, although the involvement of carbenes (or carbenoids) in these reactions has been questioned.[5]

Within our studies aimed toward the development of new synthetic applications of iodonium ylides, we anticipated that various α-substituted pyrroles could be easily obtained from an alkenyl C−H insertion of an iodonium ylide into a pyrrole moiety. Such pyrrole units constitute the core moiety of amtolmetin guacil (**1**)[6] and tolmetin (**2**),[7] important nonste-

(1) For general references on synthetic applications of carbenes (or carbenoids), see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269. (b) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811−10843. (c) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (d) Hudlicky, T. *Chem. Rev.* **1989**, *89*, 1467−1486.

(2) (a) Koser, G. F. In *The Chemistry of Functional Groups, Supplement D*; Wiley: New York, 1983. (b) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers: New York, 1992. (c) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997.

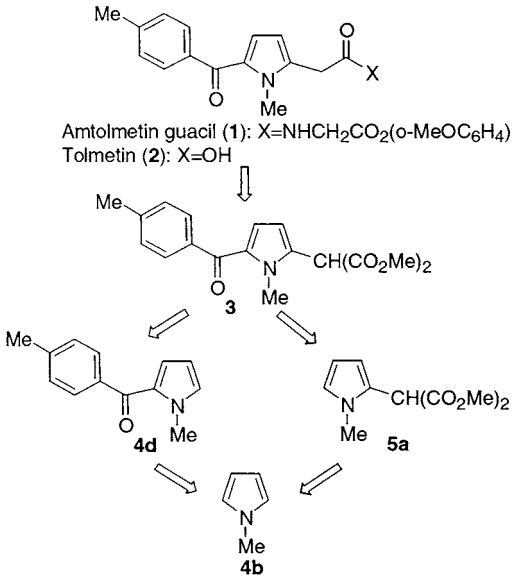
(3) (a) Schank, K.; Lick, C. *Synthesis* **1983**, 393−395. (b) Hadjiarapoglou, L.; Varvoglis, A.; Alcock, N. W.; Pike, G. A. *J. Chem. Soc., Perkin Trans. 1* 1988, 2839−2846.

(4) (a) Hadjiarapoglou, L. P. *Tetrahedron Lett.* **1987**, *28*, 4449−4450. (b) Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947−958. (c) Hadjiarapoglou, L. P.; Schank, K. *Tetrahedron* **1997**, 53, 9365−9376. (d) Asouti, A.; Hadjiarapoglou, L. P. *Tetrahedron Lett.* **1998**, *39*, 9073−9076. (e) Muller, P.; Baud, C.; Naegeli, I. *J. Phys. Org. Chem.* **1998**, *11*, 597−601. (f) Müller, P.; Boléa, C. *Synlett* **2000**, 826−828. (g) Müller, P.; Boléa, C. *Molecules* **2001**, *6*, 258−266. (h) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093−1111. (i) Georgakopoulou, G.; Kalogiros, C.; Hadjiarapoglou, L. P. *Synlett* **2001**, 1843−1846. (j) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2002**, *85*, 493−494. (k) Batsila, C.; Kostakis, G.; Hadjiarapoglou, L. P. *Tetrahedron Lett.* **2002**, *43*, 5997−6000.

10.1021/ol0343008 CCC: $25.00 
**Published on Web 04/05/2003**

roidal antiinflammatory agents. Both amtolmetin guacil and tolmetin can, in principle, be synthesized from the malonate derivative **3** (Scheme 1).

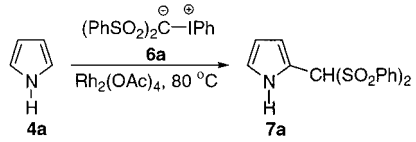
**Scheme 1**



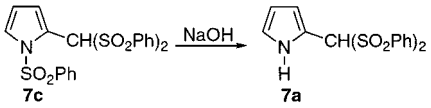

This would require the monohydrolysis of the diester moiety followed by decarboxylation of the acid. Malonate **3** could be in turn prepared from *N*-methylpyrrole **5** by α-aroylation or from α-aroylpyrrole **4d**. Both pyrrole derivatives **4d** and **5** could be synthesized from *N*-methylpyrrole **4b**. Previous studies[8] toward the synthesis of these drugs have shown that the use of a diazo precursor, as a source of acetate or a malonate substituent, leads to the isolation of nonseparable mixtures of α- and *β*-substituted pyrroles.

We now disclose that the reaction of various iodonium ylides with pyrroles affords exclusively α-substituted pyrroles with good yields. Phenyliodonium bis(phenylsulfonyl)-methylide (**6a**) was first examined, since it is a well-known[9] precursor of bis(phenylsulfonyl)methylene, especially under photochemical or Cu-catalyzed activation. The $Rh_2(OAc)_4$-catalyzed thermal reaction of phenyliodonium bis(phenylsulfonyl)methylide (**6a**) with pyrrole (**4a**) to afford α-substituted pyrrole **7a** is typical (Scheme 2). To probe the steric effects of the nitrogen substituent further, *N*-methyl- or *N*-phenylsulfonyl pyrroles **4b** and **4c** were subjected to reaction with ylide **6a** (Table 1). But the yield of the reaction was not improved. However, under photochemical activation (400 W Hg street lamp, medium pressure), the yield of **7c** was improved significantly (79% vs 33%). The *β*-isomer was not detected, although it was anticipated[10] that the *N*-phenylsulfonyl substituent should deactivate the α-position (relative to *β*-position). The *N*-phenylsulfonyl group of pyrrole **7c**, having served its purpose, was removed (Scheme 3) by treatment of pyrrole **7c** with 5 N NaOH in boiling methanol to yield pyrrole **7a** quantitatively.

**Scheme 2**




**Scheme 3**




Other examples[11] of this alkenyl C−H insertion protocol are compiled in Table 1. This α-C−H insertion reaction has been shown to be general for sulfonyl-, carbonyl-, or ester-substituted iodonium ylides. In the case of phenyliodonium acetylmethoxycarbonylmethylide (**6b**), its $Rh_2(OAc)_4$-catalyzed reaction with pyrrole (**4a**) yields the α-isomer **7d** in 53% yield. Due to the keto substituent, isomer **7d** appears as a 18:82 mixture of keto and enol forms (**7d**/**8d** = 18:82). A nitrogen substituent, i.e., methyl such as in pyrrole **4b**, results in the isolation of the corresponding α-isomer in much lower yield (23%).

Although this might be due to steric hindrance, this is not general, especially for phenyliodonium bis(methoxycarbonyl)methylide (**6c**). Its $Rh_2(OAc)_4$-catalyzed reaction with pyrrole (**4a**) yields 2-bis(methoxycarbonyl)methyl pyrrole (**5a**) in 56% yield. Several reaction conditions were examined with *N*-methylpyrrole (**4b**), and it was found that, as in our earlier studies, the use of $Rh_2(OAc)_4$ as catalyst gave the best results; however, the noncatalyzed reaction gave superior results (Table 1). This reaction proceeds even at room

(5) (a) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc*. **1989**, *111*, 6443−6444. (b) Moriarty, R. M.; Kim, J.; Guo, L. *Tetrahedron Lett*. **1993**, *34*, 4129−4132. (c) Spyroudis, S.; Tarantili, P. *J. Org. Chem*. **1993**, *58*, 4885−4889. (d) Moriarty, R. M.; May, E. J.; Prakash, O. *Tetrahedron Lett*. **1997**, *38*, 4333−4336. (e) Moriarty, R. M.; May, E. J.; Guo, L.; Prakash, O. *Tetrahedron Lett*. **1998**, *39*, 765−766. (f) Alexiou, I.; Gogonas, E. P.; Hadjiarapoglou, L. P. *Synlett* **1999**, 1925−1926. (g) Gogonas, E. P.; Hadjiarapoglou, L. P. *Tetrahedron Lett*. **2000**, *41*, 9299−9302. (h) Adam, W.; Bosio, S.; Gogonas, E. P.; Hadjiarapoglou, L. P. *Synthesis* **2002**, 2084−2090.

(6) Amtolmetin guacil is a novel drug for the treatment of osteoarthritis, rheumatoid arthritis, and postoperative pain.

(7) Tolmetin is used for the treatment of arthritis, and its sodium salt is sold by McNeil Pharmaceuticals under the registered tradename Tolectin.

(8) (a) Maryanoff, B. E. *J. Org. Chem*. **1982**, *47*, 3000−3002. (b) Maryanoff, B. E. *J. Org. Chem*. **1979**, *44*, 4410−4419.

(9) (a) Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *J. Am. Chem. Soc*. **1985**, *107*, 7178−7179. (b) Hadjiarapoglou, L.; Varvoglis, A. *J. Heterocycl. Chem*. **1988**, 25, 1599−1600. (c) Hadjiarapoglou, L.; Varvoglis, A. *Synthesis* **1988**, 913−915. (d) Hadjiarapoglou, L.; Varvoglis, A. *J. Chem. Res*. **1989**, 306. (e) Hadjiarapoglou, L.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 379−382.

(10) (a) Rokash, J.; Hamel, P.; Kakushima, M. *Tetrahedron Lett*. **1981**, *22*, 4901−4904. (b) Kakushima, M.; Hammel, P.; Frenette, R.; Rokash, J. *J. Org. Chem*. **1983**, *48*, 3214−3219. (c) Cadamuro, M.; Degani, I.; Dughera, S.; Fochi, R.; Gatti, A.; Piscopo, L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 273−283. (d) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353−364.

**Table 1.** Alkenyl C−H Insertion[a] of Iodonium Ylides **6** with Pyrroles **4**

| | | substituents | | | | | reaction conditions | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| entry | ylide | EWG[1] | EWG[2] | $R^1$ | $R^2$ | pyrrole | method | $T$ (°C) | time (min) | products [yield[b] (%)] |
| 1 | **6a** | $PhSO_2$ | $PhSO_2$ | H | H | **4a** | A | 80 | 5 | **7a** (33) |
| 2 | **6a** | $PhSO_2$ | $PhSO_2$ | Me | H | **4b** | B | reflux | 10 | **7b** (31) |
| 3 | **6a** | $PhSO_2$ | $PhSO_2$ | $PhSO_2$ | H | **4c** | B | reflux | 90 | **7c** (33) |
| 4 | **6a** | $PhSO_2$ | $PhSO_2$ | $PhSO_2$ | H | **4c** | C | r.t. | 360 | **7c** (79) |
| 5 | **6b** | MeCO | $MeO_2C$ | H | H | **4a** | A | 95 | 2 | **7d** (53) [**7d**/**8d** = 18:82] |
| 6 | **6b** | MeCO | $MeO_2C$ | Me | H | **4b** | A | 95 | 2 | **7e** (23) [**7e**/**8e** = 13:87] |
| 7 | **6c** | $MeO_2C$ | $MeO_2C$ | H | H | **4a** | A | 100 | 2 | **5a** (56) |
| 8 | **6c** | $MeO_2C$ | $MeO_2C$ | Me | H | **4b** | A | 100 | 2 | **5b** (66) |
| 9 | **6c** | $MeO_2C$ | $MeO_2C$ | Me | H | **4b** | B | 105 | 2 | **5b** (53) |
| 10 | **6c** | $MeO_2C$ | $MeO_2C$ | Me | H | **4b** | D | 105 | 2 | **5b** (81) |
| 11 | **6c** | $MeO_2C$ | $MeO_2C$ | Me | pTolCO | **4d** | A | 110 | 2 | **5d** (44), **9d** (26) |

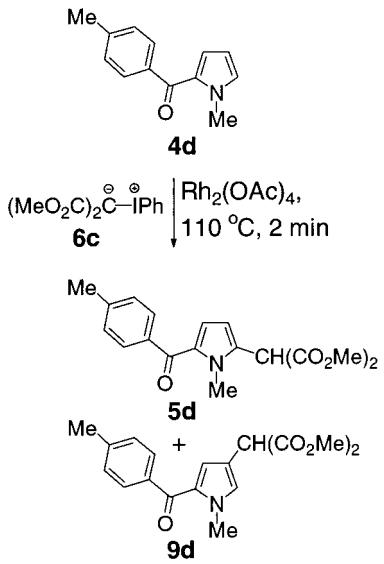
[a] All reactions were performed by heating a mixture of the iodonium ylide **6** (1.0 mmol), pyrrole **4** (4.0 mmol), and $Rh_2(OAc)_4$ (0.02 mol %) at 80−115 °C for 1−5 min (method A); by heating at reflux a mixture of the iodonium ylide **6** (1.0 mmol), pyrrole **4** (4.0 mmol), $Cu(acac)_2$ (0.02 mol %), and chloroform (10 mL) for 10−90 min (method B); by irradiating (400 W Hg street lamp, medium pressure) a suspension of iodonium ylide **6** (1.0 mmol), pyrrole **4** (4.0 mmol), and acetonitrile (10 mL) for 90 min (Method C); or by heating a mixture of the iodonium ylide **6** (1.0 mmol) and pyrrole **4** (4.0 mmol) at 115 °C for 2 min (method D). [b] Yield of isolated product after column chromatography.

temperature in 51% yield, without any catalyst, but at prolonged reaction times (12 h). Ylide **6c** is inert toward *N*-phenylsulfonylpyrrole (**4c**) even under our optimal photochemical conditions, its decomposition product, namely tetramethoxycarbonylethylene, was isolated instead. Presumably, this reaction is very sensitive to the electron deactivation of the pyrrole nucleus.

2-Pyrrolyl malonates have been obtained by the reaction[12] of bis(methoxycarbonyl)carbene, generated through Cu-catalyzed decomposition of the related thiophenium ylide, with pyrrole and by the base-catalyzed reaction[13] of di-*tert*-butyl dicarbonate with a [bis(alkoxycarbonyl)pyrrol-2-yl]-acetic acid ester. 5-Benzoylpyrrol-2-yl malonate derivatives are efficiently converted into the powerful analgesic ketorolac in two steps.[14]

The reaction of *N*-methyl-5-(*p*-methylbenzoyl) pyrrole (**4d**) with iodonium ylide **6c** represents a potentially useful route to tolmetin and amtolmetin guacil. The $Rh_2(OAc)_4$-catalyzed reaction leads to isolation of *N*-methyl-5-bis(methoxycarbonyl)methyl-2-(*p*-methylbenzoyl)pyrrole (**5d**) and *N*-methyl-4-bis(methoxycarbonyl)methyl-2-(*p*-methylbenzoyl)pyrrole (**9d**) in 44% and 26% yield, respectively (Scheme 4).

**Scheme 4**




Alternatively, pyrrole **5d** could be synthesized in 40% yield by the smooth reaction[15] of *p*-methylbenzoyl chloride with pyrrole **5a** in the presence of zinc metal.

(11) All new compounds have been fully characterized by spectral data and elemental analyses. **Representative Experimental Procedure**. Synthesis of **7a**: A suspension of iodonium ylide **6a** (0.5 g, 1.0 mmol), pyrrole (**4a**) (1.0 mL), and $Rh_2(OAc)_4$ (0.02 mol %) was heated at 80 °C for 5 min. The excess pyrrole was evaporated under reduced pressure, and the reaction residue was chromatographed (flash silica gel; $CH_2Cl_2$) to afford 2-bis(phenylsulfonyl)methylpyrrole (**7a**) as white crystals (119 mg, 33% yield): mp 154−155 °C ($CHCl_3$−petroleum ether); IR (KBr) 3440 $cm^{-1}$, 3100, 2980, 1460, 1345, 1330, 1290, 1175, 1130, 1095, 1080, 1040, 1000, 845, 790, 780, 765, 740; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.50 (s, 1H), 5.77−5.78 (m, 1H), 5.99 (dd, $J$ = 2.7, 6.2 Hz, 1H), 6.91 (dd, $J$ = 2.7, 4.2 Hz, 1H), 7.43−7.44 (m, 4H), 7.59−7.63 (m, 2H), 7.68−7.71 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 82.0 (+), 109.3 (+), 113.3, 115.9 (+), 122.0 (+), 128.9 (+), 129.0 (+), 134.5 (+), 138.1. Anal. Calcd for $C_{17}H_{15}NO_4S_2$: C, 56.49; H, 4.18; N, 3.88; S, 17.74. Found: C, 56.25; H, 4.24; N, 3.91; S, 17.44. Synthesis of **7c**: A suspension of iodonium ylide **6a** (1.0 g, 2.0 mmol) and *N*-phenylsulfonylpyrrole (**4c**) (1.65 g, 8.0 mmol) in acetonitrile (10 mL) was irradiated (400 W Hg street lamp, medium pressure) for 6.0 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed (flash silica gel, $CH_2Cl_2$−EtOAc) to afford *N*-phenylsulfonyl-2-bis(phenylsulfonyl)methylpyrrole (**7c**) as white crystals (800 mg, 79% yield): mp 142−143 °C (EtOH); IR (KBr) 3120 $cm^{-1}$, 3060, 2930, 1580, 1445, 1370, 1340, 1325, 1310, 1290, 1195, 1185, 1170, 1145, 1100, 1080, 1060, 1010, 1000, 840, 800, 780; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.33 (t, $J$ = 3.5 Hz, 1H), 6.93−6.95 (m, 2H), 7.13 (dd, $J$ = 1.5, 3.2 Hz, 1H), 7.45−7.54 (m, 6H), 7.57−7.67 (m, 3H), 7.76−7.82 (m, 6H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 78.7, 112.9, 118.2, 120.9, 126.0, 128.9, 129.4, 129.6, 134.4, 134.6, 137.8, 138.4. Anal. Calcd for $C_{23}H_{19}NO_6S_3$: C, 55.07; H, 3.82; N, 2.79. Found: C, 54.98; H, 3.70; N, 2.90.

(12) (a) Cuffe, J.; Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1978**, 641−642. (b) Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1979**, 50−51.

(13) Brysou, T. A.; Roth, G. A.; Liu, J. *Tetrahedron Lett.* **1986**, *27*, 3685−0000.

(14) (a) Artis, D. R.; Cho, I.-S.; Muchowski, J. M. *Can. J. Chem.* **1992**, *70*, 1838. (b) Schloemer, G. C.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 5230−5234.

(15) Yadav, J. S.; Reddy, B. V. S.; Kondaji, G.; Rao, S. R.; Kumar, P. S. *Tetrahedron Lett.* **2002**, *43*, 8133−8135.

Mechanistically, if we assume that a carbene (or a carbenoid) is generated, then one can rationalize the alkylation products as having arisen from either a zwitterionic or a cyclopropane intermediate. A zwitterionic route would have the electrophilic carbenoid attacking the pyrrole to give a dipolar intermediate, which could rearomatize to the alkylation product. The second possibility involves the addition of the carbenoid across a $\pi$-bond of the pyrrole to give a cyclopropane intermediate, which then unravels and rearomatize to the alkylation product. This matter may be complicated, however, if the cyclopropane is formed in a stepwise fashion; the cyclopropane pathway merges into the dipolar mechanism. A third possibility involves the initial formation of a nitrogen ylide, which is rather unstable and decomposed into the 2-alkylation products.

Also, one can rationalize an iodonium ylide either as a precursor to a carbene (or carbenoid) or a zwitterionic compound. The carbene pathway needs the cleavage of the $I-C_{carbanionic}$ bond to occur first. The second possibility resembles an iodonium ylide either as a good nucleophile possessing a potential leaving group or as a good electrophile, which could bring the substrate and the carbanionic site close together. Experimentally it is known that the nucleophilic reactivity of the iodonium ylide is rather low because its negatively charged site is sterically hindered and electronically deactivated by the electron-withdrawing substituents, while the known X-rays of iodonium ylides revealed a naked phenyliodine center (electrophile).

Despite these mechanistic implications, a unique synthesis of 2-pyrrolyl malonates has been developed from the alkenyl C−H insertion of an iodonium ylide into pyrroles. This methodology can be utilized as short syntheses of various antiinflammatory and analgesic agents of considerable potency, prepared previously via multistep synthesis.

**Acknowledgment.** We thank Prof. Dr. W. Adam (University of Würzburg) and Prof. Dr. A. de Meijere (University of Göttingen) for their generous support. G.K. thanks the Stavrou Foundation for a Master fellowship. E.P.G. thanks INTEREG-II (Prof. M. Karayiannis, University of Ioannina) for a 1-year doctoral fellowship.

OL0343008