JOC Note
pubs.acs.org/joc

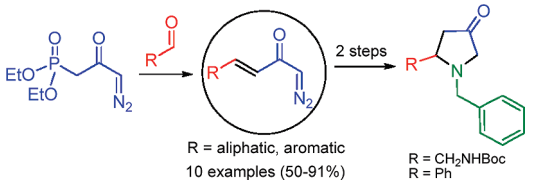
Preparation of α,β-Unsaturated Diazoketones Employing a Horner−Wadsworth−Emmons Reagent

Vagner D. Pinho and Antonio C. B. Burtoloso*

Instituto de Química de São Carlos, Universidade de São Paulo, CEP 13560-970, São Carlos, SP, Brazil

antonio@iqsc.usp.br

Received September 3, 2010



A new method for the preparation of α,β-unsaturated diazoketones from aldehydes and a Horner−Wadsworth−Emmons reagent is reported. The method was applied to the short synthesis of two substituted pyrrolidines.

The chemistry of diazo compounds has shown, over the years, a multitude of applications in the field of organic synthesis.[1−5] Some of these applications include the insertion of diazocarbonyl compounds into C−H and X−H (X = N, O, S, P, Se) bonds, cyclopropanation reactions, dipolar cycloadditions, ylide formation, and the Wolff rearrangement. In view of the wide array of transformations that diazocarbonyls can accomplish, it speaks to the importance of methods which provide these substrates efficiently and with vast structural diversity. Among the different types of diazocarbonyl substrates found in the literature to date, α,β-unsaturated diazoketones have proven to be very promising as multifunctional intermediates,[6−17] two recent examples being the asymmetric aziridination of vinyl diazoketones described by Wulff[6] and the syntheses of trisubstituted γ-butyrolactones by Brueckner.[7,8] Although there are many efficient methods to prepare diazoketones,[1,2,18] very few[19−23] can be extended to the synthesis of the α,β-unsaturated diazoketones, and this is likely responsible for their limited application in synthesis. In fact, with the exception of the Danheiser[23] deformylating procedure, none of the other methods[19−22] is general and suitable for the synthesis of unsaturated diazoketones. For example, the most useful methodology to prepare diazoketones, involving diazomethane acylation in the presence of acyl chlorides or mixed anhydrides, is not generally good for the synthesis of the α,β-unsaturated diazoketones.[19] This is because dipolar cycloaddition to the conjugated double bond rapidly occurs, resulting in the formation of pyrazolines.[24]

Herein, we present a simple procedure to prepare these unsaturated diazocarbonyl compounds from a range of aldehydes and a 3-diazo-2-oxopropylphosphonate, employing a Horner−Wadsworth−Emmons (HWE) reaction. Furthermore, we also demonstrate the utility of these unsaturated diazoketones as bifunctional building blocks by preparing two substituted pyrrolidines in just two steps.

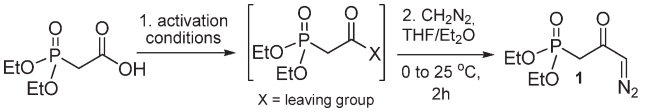
We started our work by preparing diethyl 3-diazo-2-oxopropylphosphonate **1** from (diethylphosphono)acetic acid[25] (Table 1) as described by Mikityuk[26] and with the goal to evaluate it as a new HWE diazo reagent. Unfortunately, employing Mikityuk's protocol, we could only obtain low yields of compound **1** (entry 1, Table 1). Given that no other work was described toward the preparation of **1** to date, we developed an improved synthesis as depicted in Table 1.

Diazophosphonate **1** proved to be very difficult to prepare initially. This was due to the extreme instability or lack of reactivity of the activated (diethylphosphono)acetic acids toward diazomethane. Among all the conditions described in Table 1, diazomethane acylation from an acyl chloride proved to be the best, since the other activated carboxylic acids (entries 8−12) were not suitable for this transformation. After these improvements, phosphonate **1** could be easily synthesized in 70% yield as a stable yellow oil.[27]

(1) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(2) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; New York, 1998.
(3) Singh, G. S. *Curr. Org. Synth.* **2005**, *2*, 175.
(4) Ferreira, V. F. *Curr. Org. Chem.* **2007**, *11*, 177.
(5) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.
(6) Deng, Y.; Lee, Y. R.; Newman, C. A.; Wulff, W. D. *Eur. J. Org. Chem.* **2007**, *13*, 2068.
(7) Kapferer, T.; Brueckner, R. *Eur. J. Org. Chem.* **2006**, *9*, 2119.
(8) Kapferer, T.; Brueckner, R.; Herzig, A.; Koenig, W. A. *Chem.—Eur. J.* **2005**, *11*, 2154.
(9) Cainelli, G.; Galletti, P.; Garbisa, S.; Giacomini, D.; Sartor, L.; Quintavalla, A. *Bioorg. Med. Chem.* **2003**, *11*, 5391.
(10) Rowlands, G. J.; Barnes, W. K. *Tetrahedron Lett.* **2004**, *45*, 5347.
(11) Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2003**, *9*, 1765.
(12) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, *24*, 3312.
(13) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.
(14) Ujvary, I.; Prestwich, G. D. *J. Labelled Compd. Radiopharm.* **1990**, *28*, 167.
(15) Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3625.
(16) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1990**, *55*, 311.
(17) Muller, P.; Maitrejean, E. *Collect. Czech. Chem. C.* **1999**, *64*, 1807.
(18) Maas, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186.
(19) Wotiz, J. H.; Buco, S. N. *J. Org. Chem.* **1955**, *20*, 210.
(20) Harmon, R. E.; Sood, V. K.; Gupta, S. K. *Synthesis* **1974**, *8*, 577.
(21) Regitz, M.; Menz, F.; Liedhegener, A. *Liebigs Ann. Chem.* **1970**, *739*, 174.
(22) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.
(23) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(24) Unless starting from the α,β-dialkylated or β,β-dialkylated α,β-unsaturated acids.
(25) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477–3480.
(26) Mikityuk, A. D.; Kashemirov, B. A.; Khokhlov, P. S. *Zh. Obshch. Khim.* **1987**, *57*, 1669.
(27) We exhaustively tested many classical conditions to prepare acid chlorides, but the only condition that provided acceptable yields of **1** was refluxing the carboxylic acid with freshly distilled oxalyl chloride in chloroform.

DOI: 10.1021/jo1021844 Published on Web 12/14/2010

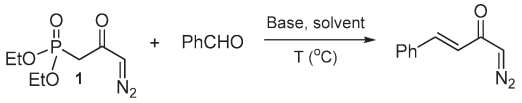
TABLE 1. Optimization Studies for the Preparation of Diazophosphonate 1



entry	activation method	activation conditions	yield (%)
1[26]	acyl chloride[a]	1. $SOCl_2$, 25 °C, 3 h	18
2	acyl chloride[a]	1. $SOCl_2$, 50 °C, 3 h	0
3	acyl chloride[a]	1. SO_2Cl_2, 25 °C, 3 h	5
4	acyl chloride[a]	2. PCl_5, THF, 25 °C, 1 h	0
5	acyl chloride[a]	1. $(COCl)_2$, 25 °C, 2 h	20
6	acyl chloride[a]	1. $(COCl)_2$, DCM, 25 °C, 2 h	25
7	acyl chloride[a]	1. $(COCl)_2$, $CHCl_3$, reflux, 2 h	70
8	acyl phosphonium[b]	1. PPh_3, NBS, THF, 0 °C, 1 h	0
9	acyl urea[b]	1. DCC, THF, 25 °C, 1 h	0
10	acyl mesylates[b]	1. MsCl, CH_3CN, TEA, 0 °C, 1 h	0
11	mixed anhydride[b,c]	1. $ClCO_2Et$, TEA, DCM, 0 °C, 1 h	0
12	mixed anhydride[b,c]	1. TFAA, $CHCl_3$, reflux, 2 h	0

[a]After the activation of (diethylphosphono)acetic acid, the solvent was concentrated and the residue dissolved in dry THF prior to its addition to a ethereal diazomethane solution (3 equiv). [b]Ethereal diazomethane solution (3 equiv) was added directly in the reaction flask after carboxylic acid activation. [c]12 h reaction after diazomethane addition.

TABLE 2. Evaluation of the HWE Reaction between Diazophosphonate 1 and Benzaldehyde



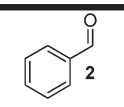
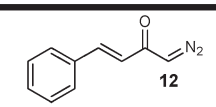
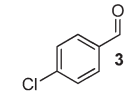
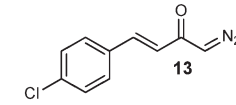
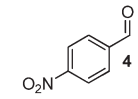
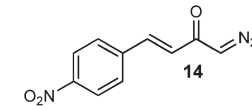
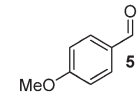
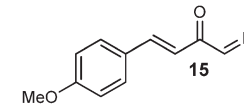
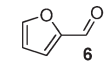
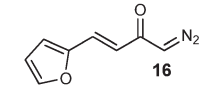
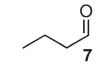
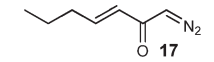
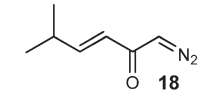
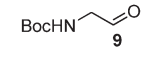
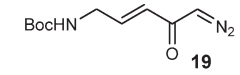
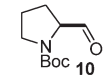
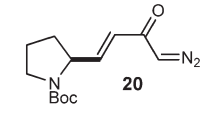
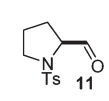
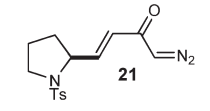
entry	method	base	solvent	*T* (°C)	yield (%)
1[a,b]	A	$Ba(OH)_2$	THF	0 (2 h)	57
2[a,c]	B	NaH	THF	−78 (1 h) to 0 (1 h)	60
3[a,c]	C	NaH	PhMe	−78 (1 h) to 0 (1 h)	62
4[a,c]	D	LiHMDS	THF	−78 (1 h) to 0 (1 h)	38
5[a,c]	E	NaHMDS	THF	−78 (1 h) to 0 (1 h)	60
6[a,c]	F	KHMDS	THF	−78 (1 h) to 0 (1 h)	56
7[a,c]	G	BuLi	THF	−78 (1 h) to 0 (1 h)	60
8[a,d]	H	DIPEA	CH_3CN	25 (24 h)	37
9[a,e]	I	K_2CO_3	THF	25 (48 h)	14
10[f]	J	NaH	THF	−78 (1 h) to 0 (1 h)	91

[a]1.0 equiv of phosphonate **1**. [b]0.8 equiv of the base. [c]1.1 equiv of the base. [d]3.0 equiv of the base and 1.0 equiv of LiCl as additive. [e]1.0 equiv of 18-crown-6 ether as additive. [f]2.0 equiv of the phosphonate **1** and 2.2 equiv of NaH.

With an improved method for the synthesis of **1** in hand, we turned our attention to find the best conditions for the Horner−Wadsworth−Emmons reaction employing phosphonate **1** and benzaldehyde as a model (Table 2). Initially, after studying some classical conditions[28−33] for the HWE reaction, we found that method B (NaH as a base) proved to be the optimal. Although methods A, C, and E−G also provided similar yields for the reaction with benzaldehyde, method B furnished the best yields when extended to other aldehydes. From Table 2, it is also clear that solvent effects had no substantial influence in the yield of the HWE reaction (entries 2 and 3), but counterion effects had (entries 4−6). Since method B provided a very clean HWE reaction, we thought that the 60% yield may be related to the degradation of phosphonate **1** during the reaction. To verify that, we decided to adjust method B by using 2 equiv of **1**. To our delight, under these conditions (entry 10), a 91% yield could be obtained for the HWE reaction.

Employing method J (2 equiv of **1**), aldehydes **2**−**11** were converted to the respective α,β-unsaturated diazoketones[34] **12**−**21** with isolated yields ranging from 50 to 91%. Table 3 illustrates these results from branched and unbranched aliphatic

TABLE 3. Synthesis of Diazoketones 12−21 from Aldehydes 2−11 and HWE Reagent 1 (Method J)

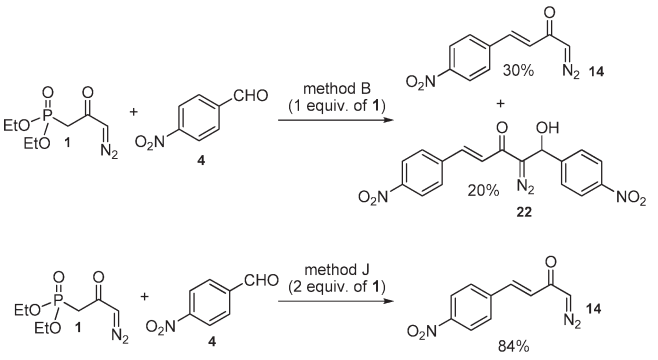
Entry	Aldehyde[a]	α,β-unsaturated diazoketone	Yield (%)[b]
1			91
2			83
3			84
4			50
5			78
6			74
7			67
8			80
9		 [α]$_D$ -74.6 (*c* 1.90, $CHCl_3$)	81
10		 [α]$_D$ -163.4 (*c* 2.10, $CHCl_3$)	58

[a]All liquid aldehydes were freshly distilled prior to use. [b]All yields refer to purified products after flash chromatography.

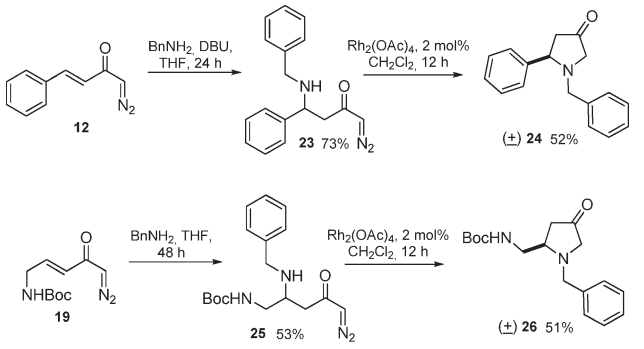
(28) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
(29) Paterson, I.; Yeung, K.; Smaill, J. *Synlett* **1993**, 774.
(30) Grison, C.; Genève, S.; Halbin, E.; Coutrot, P. *Tetrahedron* **2001**, *57*, 4903.
(31) Blanchette, M. A.; Choay, w.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(32) Lee, E. S.; Lee, W. G.; Yun, S.; Rho, S. H.; Im, I.; Yang, S. T.; Sellamuthu, S.; Lee, Y. J.; Kwon, S. J.; Park, O. K.; Jeon, E.; Park, W. J.; Kim, Y. *Biochem. Biophys. Res. Commun.* **2007**, *358*, 7–11.
(33) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967.

(34) Only the *E* isomer was detected.

SCHEME 1. Coupled Diazoketone 22 Observed when 1.0 equiv of 1 Was Employed



SCHEME 2. Synthesis of Pyrrolidines 24 and 26 from α,β-Unsaturated Diazoketones 12 and 19



aldehydes, aromatic aldehydes, and aminoaldehydes. It is interesting to note that the use of excess of the phosphonate **1** seems to be crucial for the success of these reactions. In fact, besides the formation of unsaturated diazoketones in lower yields (20−80), the use of only 1 equiv of **1** can led in some cases to the formation of coupled diazoketones.[35] This fact was observed during the HWE reaction with very reactive aldehydes such as 4-nitrobenzaldehyde (Scheme 1).

To show the applicability of the present method and another utility of this class of unsaturated diazocarbonyls, diazoketones **12** and **19** were readily converted in two steps in the functionalized pyrrolidinones **24** and **26** after Michael addition[12] in the presence of benzylamine and rhodium-catalyzed N−H insertion (Scheme 2).[36]

Pyrrolidinones such as **24** and **26** are important building blocks in the pharmaceutical industry and are highly useful synthetic intermediates to be applied in the total synthesis of natural pyrrolidines.[37−40] Furthermore a vast library of pyrrolidines can be synthesized with this method just by varying the aldehyde and amine in the HWE and Michael addition reactions, respectively. It is also noteworthy that, from α,β-unsaturated diazoketones, no nitrogen atom protection is necessary when *N*-alkylpyrrolidines are desired, a drawback that is often encountered when these compounds are prepared from amino acid-derived diazoketones.

In summary, a new method for the preparation of α,β-unsaturated diazoketones from commercially available or easily accessed aldehydes and a new Horner−Wadsworth−Emmons reagent is reported. The method can be extended to the synthesis of structurally diverse unsaturated diazoketones and will complement the Danheiser deformylating protocol. To demonstrate the application of these diazoketones, a short synthesis of two substituted pyrrolidines was also accomplished.

Experimental Section

3-Diazo-2-oxopropylphosphonate 1. (Diethylphosphono)acetic acid[25] (2.10 g, 10.8 mmol, 1 equiv) was added to a 50.0 mL flame-dried round-bottom flask, followed by the addition of dry toluene (3 × 15.0 mL) for azeothropic removal of moisture. Next, dry chloroform (27.0 mL) was added and the system cooled to 0 °C. Freshly distilled oxalyl chloride (2.83 mL, 32.4 mmol, 3 equiv) was then added dropwise to the reaction vessel and the solution stirred at reflux for 2 h. After this period, the solvent and volatiles were removed on the rotary evaporator, and the resultant residue was dissolved in dry tetrahydrofuran (THF) (11.0 mL). (*Caution: The acid chloride from* (*diethylphosphono*)*acetic acid is very unstable, and care should be exercised during these operations to avoid its hydrolysis.*) Next, the acid chloride solution was added by cannula to a cooled (0 °C) and freshly prepared 0.4 M ethereal solution of diazomethane (67.0 mL, 2.5 equiv)[41] and the reaction allowed to stir at room temperature for 2 h. After that, the solvent was removed via rotary evaporator and the residue purified by flash column chromatography (gradient 50% AcOEt/hexane and then 100% AcOEt) to furnish the diazophosphonate **1** (1.65 g, 70%) as a yellow oil:[42] ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.61 (1H, s), 4.16 (4H, m), 2.95 (2H, d, J = 21.7 Hz), 1.34 (6H, td, J = 7.0, 0.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 173.0, 145.1, 34.3, 21.4, 13.6; IR (neat, cm^{-1}) 2108, 1633, 1359, 1249, 1045, 972; HRMS (ESI) calcd for $C_7H_{13}N_2NaO_4P$ $[M + Na]^+$ 243.0511, found 243.0515; R_f 0.27 (10% MeOH/EtOAc).

General Procedure for the HWE Reaction. (*E*)-1-Diazo-4-phenylbut-3-en-2-one 12 (Method J). To a suspension of NaH (60% in mineral oil) (13.0 mg, 0.33 mmol, 2.2 equiv) in dry THF (0.5 mL), under argon atmosphere and at 0 °C, was added a 0.3 M solution of diethyl 3-diazo-2-oxopropylphosphonate (66.0 mg, 0.30 mmol, 2.0 equiv) in dry THF. After being stirred for 15 min at this temperature, the system was cooled to −78 °C, and then a 0.2 M solution of freshly distilled benzaldehyde (16.0 mg, 0.15 mmol, 1.0 equiv) in dry THF was added dropwise. After 1 h, the −78 °C cooling bath was replaced with ice−water and the mixture stirred for an additional 1 h. Next, a saturated aqueous NH_4Cl solution (10 mL) was added to the reaction vessel and the aqueous layer extracted with dichloromethane (3 × 6 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and evaporated in a rotary evaporator. Purification by flash column chromatography (12% AcOEt/Hexanes) afforded diazoketone **12** (47.0 mg, 91%) as a stable yellow solid: ^{1}H NMR (200 MHz, C_6D_6) δ 7.63 (d, J = 15.9 Hz, 1H), 7.07−6.99 (m, 5H), 6.22 (d, J = 15.9 Hz, 1H), 4.40 (s, 1H); C NMR (50 MHz, $CDCl_3$) δ 184.2, 140.7, 130.3, 128.9, 128.2, 123.6, 56.1; IR (KBr, cm^{-1})

(35) For a precedent that shows a similar type of coupling between ethyldiazoacetate and aldehydes, see: Erhunmwunse, M. O.; Steel, P. G. *J. Org. Chem.* **2008**, *73*, 8675.

(36) Desai, P.; Aubé, J. *Org. Lett.* **2000**, *2*, 1657.

(37) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: New York, 2002.

(38) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.

(39) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.

(40) Achenbach, T. V.; Slater, E. P.; Brummerhop, H.; Bach, T.; Muller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794.

(41) Very recently, a new procedure of diazoketone syntheses employing only one equivalent of diazomethane has been described: Pace, V.; Verniest, G.; Sinisterra, J.; Alcantara, A. R; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 5760.

(42) Lowering the reaction scale by too much and/or not using freshly prepared diazomethane caused the yield to drop to 46−50%.

3070, 2098, 1637, 1583, 1448, 1369, 1149, 973, 757; HRMS (ESI) calcd for $C_{10}H_9N_2O$ $[M + H]^+$ 173.0715, found 173.0712; mp 63−66 °C; R_f 0.30 (25% EtOAc/hexanes).

Acknowledgment. We thank FAPESP (Research Supporting Foundation of the State of São Paulo) for financial support and a fellowship to V.D.P. We also thank CNPq for research fellowship to A.C.B.B. and IQSC-USP for facilities (in special to Dr. Sylvana C. Miguel Agustinho). We also thank Dr. Ross Denton (University of Nottingham) for reading and discussion of the manuscript.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.