This article was downloaded by: [University of Calgary] On: 19 June 2013, At: 01:05 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/gpss20

Triphenylphosphine-Mediated Reaction Between Dimethyl Acetylenedicarboxylate and NH-Acids Derived from Diaminobenzenes

Issa Yavari ^{a b} & Leila Ahmadian-Razlighi ^c ^a Chemistry Department, Science and Research Campus, Islamic Azad University, Ponak, Tehran, Iran ^b Chemistry Department, Tarbiat Modarres University, Tehran, Iran ^c Chemistry Department, Islamic Azad University, Tehran North Branch, Tehran, Iran

Published online: 15 Aug 2006.

To cite this article: Issa Yavari & Leila Ahmadian-Razlighi (2006): Triphenylphosphine-Mediated Reaction Between Dimethyl Acetylenedicarboxylate and NH-Acids Derived from Diaminobenzenes, Phosphorus, Sulfur, and Silicon and the Related Elements, 181:4, 771-777

To link to this article: http://dx.doi.org/10.1080/10426500500271550

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <u>http://www.tandfonline.com/page/terms-and-conditions</u>

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.



Triphenylphosphine-Mediated Reaction Between Dimethyl Acetylenedicarboxylate and NH-Acids Derived from Diaminobenzenes

Issa Yavari

Chemistry Department, Science and Research Campus, Islamic Azad University, Ponak, Tehran, Iran, and Chemistry Department, Tarbiat Modarres University, Tehran, Iran

Leila Ahmadian-Razlighi

Chemistry Department, Islamic Azad University, Tehran North Branch, Tehran, Iran

 $\label{eq:product} Protonation of the 1:1 adduct produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate with ethyl 2-[(2-{[2-(ethyloxy)-2-oxoacetyl]amino]phenyl]amino]-2-oxoethanoate leads to a vinylphosphonium salt, which undergoes an intermolecular Wittig reaction to produce dimethyl 4-(acetyloxy)-1-(2-{[2-(ethyloxy)-2-oxoacetyl]amino]phenyl)-5-oxo-2, 5-dihydro-1H-pyrrole-2,3-dicarboxylate. Using ethyl 2-[(3-{[2-(ethyloxy)-2-oxoacetyl]amino]phenyl)amino]-2-oxoethanoate or ethyl 2-[(4-{[2-(ethyloxy)-2-oxoacetyl]amino]phenyl)amino]-2-oxoethanoate as an NH acid produces dimethyl 4-(acetyloxy)-1-(3-{3-(ethyloxy)-4,5-bis[(methyloxy)carbonyl]-2-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate or dimethyl 4-(ethyloxy)-1-(4-{3-(ethyloxy)-4,5-bis[(methyloxy)carbonyl]-2-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate.$

 ${\bf Keywords}$ Acetylenic ester; intramolecular Wittig rection; pyrrole derivatives; triphenylphosphine

INTRODUCTION

Simple nitrogen-containing heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores of historical importance.¹ Of these heterocycles, the synthesis, reactions, and biological activities of pyrrole-containing molecules stand as an area of research in heteroaromatic chemistry, and this structural motif appears in a large number

Received June 7, 2005; accepted June 7, 2005.

Address correspondence to Issa Yavari, Tarbiat Modarres University, Chemistry Department, PO Box 14115-175, Tehran, Iran. E-mail: yavarisa@modares.ac.ir

of pharmaceutical agents and natural products.² Accordingly, many strategies have been developed for the preparation of pyrroles.^{2,3} Fivemembered ring lactams have been used in routes to various alkaloids⁴ and are suitable precursors for γ -amino acids such as statine and its analogues.⁵ There are many examples of pyrroline-containing natural products with interesting pharmacological activates. Typical examples are the platelet aggregation inhibitor PI-091 and the antitumor alkaloide Jatropham.^{6,7} As part of our current studies on the development of new routes to heterocyclic systems,⁸ we now report that the reaction of dimethyl acetylenedicarboxylate (DMAD) with ethyl 2-[2-{[2-(ethyloxy)-2-oxoacety)]amino}phenyl}amino]-2-oxoethanoate (1) in the presence of triphenylphosphine leads to dimethyl 4-(acetyloxy)-1-(2-{[2-(ethyloxy)-2-oxoacetyl]amino}-phenyl)-5-oxo-2,5-dihydro-1 Hpyrrole-2,3-dicarboxylate (2) in a 72% yield (Scheme 1). Attempts to construct another 5-oxo-2,5-dihydro-1 H-pyrrole moiety by reacting 2 with DMAD and triphenylphosphine were unsuccessful.



SCHEME 1

RESULTS AND DISCUSSION

The reaction of DMAD with 1 in the presence of triphenylphosphine proceeded spontaneously room temperature in CH_2Cl_2 and was finished within 24 h. ¹H and ¹³C NMR spectra of the crude products clearly indicated the formation of 2. Any product other than 2 could not be detected by NMR spectroscopy.

Reactions are known in which an unsaturated heterocyclic compound is produced from a phosphorane connected with a carbonyl group by a chain containing a heteroatom.^{8–10} Thus, the 2.5-dihydropyrrole derivative 2 may be regarded as the product of an intramolecular Wittig reaction.¹⁰ Such an addition-cyclization product apparently results from an initial addition of triphenylphosphine to DMAD and the subsequent protonation of the 1:1 adduct 3 by 1 (Scheme 2). Then the positively charged ion 4 is attacked by the nitrogen atom of the conjugated base of the NH-acid to form the phosphorane **6**, which is converted to the 2,5-dihydropyrrole derivative **2**.



SCHEME 2

The structure of 2 was deduced from its elemental analyses and its IR, ¹H, and ¹³C NMR spectra. The mass spectrum of this compound confirms its molecular weight. Initial fragmentation involves the loss from or the complete loss of the side chains and the scission of the heterocyclic ring system.

The ¹H NMR spectrum of **2** exhibits three sharp lines for methoxy ($\delta = 3.61$ and 3.84 ppm) and methine ($\delta = 5.31$ ppm) protons. The aryl moiety shows characteristic signals in the appropriate region of the spectrum. The ¹³C NMR spectrum of **2** shows 18 sharp signals in agreement with the proposed structure.

When the reaction between DMAD and triphenylphosphine was carried out in the presence of ethyl 2-[(3-{[2-(ethyloxy)-2-oxoacetyl]-amino}phenyl)amino]-2-oxoethanoate (7) or ethyl 2-[(4-{[2-(ethyloxy)-2-oxoacetyl]amino}phenyl)amino]-2-oxoethanoate (9) as an NH-acid, the corresponding dimethyl 4-(acetyloxy)-1-(3-3-(ethyloxy)-4,5-bis[(methyloxy)carbonyl]-2-oxo-2,5-dihydro-1H-pyrrol-1-yl}phenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate (8) or dimethyl 4-(ethyloxy)-1-(4-{3-(ethyloxy)-4,5-bis[(methyloxy) carbonyl]-2-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylate (10) was obtained in good yield (see Scheme 3).

The ¹ H and ¹³C NMR spectra of **8** and **10** are similar to those of **2**. The proposed structures for these compounds were confirmed by their elemental analyses and IR spectra. The mass spectra of these isomeric structures are fairly similar and confirm their molecular weights.



SCHEME 3

In conclusion, the presented reaction gives a simple one-pot entry into the synthesis of polyfunctionalized 5-oxo-2,5-dihydro-1*H*-pyrrole derivatives of potential synthetic interest.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The NMR spectra were recorded at 300 (¹H) and 75 (¹³C) MHz on a Bruker Avance DPX-300 MHz NMR instrument with CDCl₃ as a solvent. Chemical shifts (δ) are reported relative to TMS as the internal standard. The reagents and solvents used in this work were obtained from Fluka and used without further purification.

Preparation of 1,7, and 9 Examplified on Ethyl 2-[(2-{[2-(Ethyloxy)-2-oxoacetyl]amino}phenyl}amino]-2-oxoethanoate (1): Typical Procedure

To a stirred solution of 1,2-diaminobenzene (1.08 g, 10 mmol) in dry diethyl ether (30 mL) was added, dropwise, a solution of ethyl oxalyl chloride (3.0 g, 22 mmol) in 10 mL of dry diethyl ether at 10°C over 10 min. The reaction mixture was allowed to stand at r.t. for 24 h. The solvent was removed under reduced pressure and the viscous residue was crystallized from ethanol to produce 1 as pale yellow crystals; m.p. 162–165°C; yield: 2.7 g (87%). IR (KBr) (ν_{max} /cm⁻¹): 3305 (N–H), 1720 and 1728 (C=O). ¹H NMR (300 MHz, CDCl₃): $\delta_{\rm H} = 1.44$ (6 H, t, ³ $J_{\rm HH} = 7.2$ Hz, 2 CH₃), 4.43 (4 H, q, ³ $J_{\rm HH} = 7.2$ Hz, 2 OCH₂), 7.34–7.76 (4 H, m, C₆H₄), 9.32 (2 H, s, 2 NH) ppm. ¹³C NMR (75.5 MHz, CDCl₃): $\delta_{\rm C} = 14.3$ (2 CH₃), 64.2 (2 OCH₂), 125.3 (2 CH), 127.8 (2 CH), 129.2 (2 C), 155.4 (2 C=O), 160.6 (2 C=O) ppm.

Ethyl 2-[(3-{[2-(Ethyloxy)-2-Oxoacetyl]amino}phenyl)amino]-2-oxoethanoate (7)

Pale yellow crystals; m.p. 121–123°C; yield: 2.8 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3301 (N–H), 1718 and 1723 (C=O). ¹H NMR (300 MHz, CDCl₃): $\delta_{\rm H} = 1.38$ (6 H, t, ³ $J_{\rm HH} = 7$ Hz, 2 CH₃), 4.38 (4 H, q, ³ $J_{\rm HH} = 7$ Hz, 2 OCH₂) 7.34–7.53 (3 H, m, 3 H of C₆H₄), 8.03 (1 H, t, ⁴ $J_{\rm HH} = 2$ Hz, H of C₆H₄), 9.09 (2 H, s, 2 NH) ppm. ¹³C NMR (75.5 MHz, CDCl₃): $\delta_{\rm C} = 14.3$ (2 CH₃), 64.2 (2 OCH₂), 111.6 (2 CH), 117.2 (CH), 130.4 (CH), 137.5 (2 C), 154.5 (2 C=O), 161.1 (2 C=O) ppm.

Ethyl 2-[(4-{[2-(Ethyloxy)-2-oxoacetyl]amino}phenyl)amino]-2-oxoethanoate (9)

Pale yellow crystals; m.p. 203–205°C; yield: 2.9 g (93%).

IR (KBr) (ν_{max} /cm⁻¹): 3304 (N–H), 1714 and 1725 (C=O). ¹H NMR (300 MHz, CHCl₃): $\delta_{\text{H}} = 1.45$ (6 H, t, ³ $J_{\text{HH}} = 7.2$ Hz, 2 CH₃), 4.45 (4 H, q, ³ $J_{\text{HH}} = 7.2$ Hz, 2 OCH₂), 7.69 (4 H, s, C₆H₄), 8.91 (2 H, s, 2 NH) ppm. ¹³C NMR (75.5 MHz, CDCl₃.): $\delta_{\text{C}} = 14.3$ (2 CH₃), 64.2 (2 OCH₂), 120.9 (4 CH), 134.0 (2 C), 154.1 (2 C=O), 161.3 (2 C=O) ppm.

Preparation of 2, 8, and 10 Examplified on Dimethyl 4-(Acetyloxy)-1-(2-{[2-ethyloxy)-2-oxoacetyl]amino}phenyl)-5-oxo-2,5dihydro-1H-pyrrole-2,3-dicarboxylate(2): Typical Procedure

To a stirred solution of 1 (0.6 g, 2 mmol) and triphenylphosphine (0.52 g, 2 mmol), in 10 mL of toluene was added, dropwise, a solution of DMAD (0.28 g, 2 mmol) in 5 mL of toluene at 20°C over 10 min. The reaction

mixture was refluxed for 8 h. The solvent was removed under reduced pressure and the viscous residue was purified by preparative TLC on silica gel (Merck silica gel DC-Fertigplatten 60/Kieselgur F₂₅₄) 20×20 cm plates using CHCl₃ and EtOAc (10:1) as an eluent. Zones were detected by the quenching of indicator fluorescence upon exposure to 366 nm of UV light. The product was obtained by the extraction of the silica gel with CH_2Cl_2 to produce a yellow powder; m.p. 120–123°C; yield: 0.6 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 1644 and 1717 (C=O). ¹H NMR (300 MHz, CHCl₃): $\delta_{\rm H} = 1.43$ (3 H, t, ³ $J_{\rm HH} = 7.1$ Hz, CH₃), 1.49 (3 H, t, ${}^{3}J_{HH} = 7.1$ Hz, CH₃), 3.61 (3 H, s, OCH₃), 3.84 (3H, s, OCH₃), 4.42 (2 H, q, ${}^{3}J_{HH} = 7.1$ Hz, OCH₂), 4.86 (2 H, q, ${}^{3}J_{\rm HH} = 7.1$ Hz, OCH₂), 5.31 (1 H, s, CH), 7.29–7.43 (3 H, m, 3 H of C₆H₄), 8.20 (1 H, d, ${}^{3}J_{HH} = 8.0$ Hz, H of C₆H₄), 9.42 (1H, s, NH) ppm. ¹³C NMR (75.5 MHz, CDCl₃): $\delta_{\rm C} = 14.3$ (CH₃), 16.1 (CH₃), 52.5 (OCH₃) 53.8 (OCH₃), 62.8 (OCH₂), 63.9 (CH), 69.2 (OCH₂), 113.9 (O-C=C), 124.9 (CH), 126.8 (CH), 126.9 (CH 127.4 (CH), 130.1 (C), 133.6 (C) 153.7 (O–C=C), 154.8 (C=O), 160.7 (C=O), 162.3 (C=O), 164.3 (C=O), 168.45 (C=O) ppm. MS (El, 70 eV): m/z (%) = 436 (M⁺ + 1, 7), 326 (100), 298 (74), 230 (58), 57 (47), 41 (38). Anal. calcd. of C₂₀H₂₂N₂O₉ (436.4): C, 55.04; H, 5.54; N, 6.42. Found: C, 55.26; H, 5.71; N, 6.46%.

Dimethyl 4-Etyloxy-1-{3-[3-ethyloxy-4,5-bis(methyloxycarbonyl)-2-oxo-2,5-dihydro-1H-pyrrol-1-yl]phenyl}-5-oxo-2,5dihydro-1*H*-pyrrole-2,3-dicarboxylate (8)

Yellow powder; m.p. 111–114°C; yield: 0.66 g (60%). IR (KBr) (ν_{max}/cm^{-1}): 1651 and 1715 (C=O). ¹H NMR (300 MHz, CHCl₃): $\delta_{\rm H}$ = 1.43 (6 H, t, ³ $J_{\rm HH}$ = 7.2 Hz, 2 CH₃), 3.68 (6 H, s, 2 OCH₃), 3.82 (6 H, s, 2 OCH₃), 4.80 (4 H, q, ³ $J_{\rm HH}$ = 7.2 Hz, 2 OCH₂), 5.37 (2 H, s, 2 CH), 7.42–7.47 (3 H, m, 3 H of C₆H₄), 7.90 (1 H, t, ⁴ $J_{\rm HH}$ = 2 Hz, H of C₆H₄), ppm. ¹³C NMR (75.5 MHz, CDCl₃): $\delta_{\rm C}$ = 16.1 (2 CH₃), 52.5 (2 OCH₃), 53.6 (2 OCH₃), 61.2 (2 CH), 69.3 (2 OCH₂), 112.2 (O–C=C), 114.9 (2 CH), 119.4 (CH), 130.4 (CH), 137.7(2 C), 154.5 (2 O–C=C), 162.0 (C=O), 164.0 (C=O), 168.4 (C=O) ppm. MS (El, 70 eV): m/z (%) = 562 (M⁺ + 1, 7), 326 (100), 298 (74), 230 (58), 57 (47), 41 (38). Anal. calcd. for C₂₆H₂₈N₂O₁₂ (562.5): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.68; H, 5.01; N, 5.02%.

Dimethyl 4-Ethoxy-1-{4-[3-ethoxy-4,5-bis(methoxycarbonyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-1-Yl]phenyl}-5-oxo-2,5dihydro-1*H*-pyrrole-2,3-dicarboxylate (10)

Yellow powder; m.p. 117–120°C; yield: 0.7 g (63%). IR (KBr) (ν_{max} /cm⁻¹): 1648 and 1717 (C=O). ¹H NMR (300 MHz, CHCl₃): $\delta_{H} = 1.42$ (6 H, t,

 ${}^{3}J_{\rm HH} = 7.2$ Hz, 2 CH₃), 3.65 (6 H, s, 2 OCH₃), 3.88 (6 H, s. 2 OCH₃), 4.81 (4 H, q, ${}^{3}J_{\rm HH} = 7.2$ Hz, 2 OCH₂), 5.35 (2H, s, 2 CH) 7.62 (4 H, s, C₆H₄) ppm. 13 C NMR (75.5 MHz, CDCl₃): $\delta_{\rm C} = 16.0$ (2 CH₃), 52.4 (2 OCH₃), 53.5 (2 O CH₃), 61.1 (2 CH), 62.2 (2 OCH₂), 112.1 (2 O–C=C), 122.3 (4 CH), 134.6 (2 C), 154.6 (2 O–C=C), 162.4 (C=O), 163.9 (C=O), 168.4 (C=O) ppm. MS (El, 70 eV): m/z (%) = 562 (M⁺ + 1, 7), 326 (100). 298 (74), 230 (58), 57 (47), 41 (38). Anal. Calcd. for C₂₆H₂₈N₂O₁₂ (562.5): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.74; H, 5.05; N, 5.04%.

REFERENCES

- F. S. Yates, In Comprehensive Heterocyclic Chemistry, A. J. Boulton and A. McKillop, Eds. (Pergamon, Oxford, 1984), Vol. 2, p. 511.
- [2] R. A. Jones, In Pyrroles, Part II: The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles (Wiley, New York, 1992).
- [3] T. L. Gilchrist, J. Chem. Soc., Perkin Trans. 1, 2491 (2001).
- [4] G. Casiraghi, P. Spanu, G. Rassu, L. Pinna, and F. Ulgheri, J. Org. Chem., 59, 2906 (1994).
- [5] (a) B. D. Griffart and N. Langois, *Tetrahedron Lett.*, **35**, 119 (1994); (b) P. Jouin and B. Castro, J. Chem. Soc., *Perkin Trans.* 1, 1177 (1987).
- [6] D. Ma, J. Ma, W. Ding, and L. Dal, Tetrahedron Asymmetry, 7, 2365 (1996).
- [7] J. P. Dittami, F. Xu, H. Qi, and M. W. Martin, Tetrahedron Lett., 36, 4210 (1995).
- [8] (a) I. Yavari, R. Hekmat-Shoar, and A. Zonouzi, Tetrahedron Lett., 39, 2391 (1998); (b) I. Yavari and F. Nourmohammadian, J. Chem. Res. (S), 512 (1999); (c) I. Yavari and S. Asghari, Tetrahedron, 55, 11853 (1999); (d) I. Yavari, M. Adib, and M. Esnaashari, Monatsh Chem., 132, 1557 (2001); I. Yavari and M. Bayat, Tetrahedron, 59, 2001 (2003), (e) I. Yavari and M. Adib, *Tetrahedron*, 57, 5873 (2001); (f) I. Yavari, M. Adib, and L. Hojabri, Tetrahedron, 57, 7537 (2001); (g) I. Yavari, M. Adib, and M. H. Sayahi, Tetrahedron Lett., 43, 2927 (2002); (h) I. Yavari, M. Adib, and M. H. Sayahi, J. Chem. Soc., Perkin Trans. 1, 1517 (2002): (i) I. Yavari, M. Adib, and F. Jahani-Moghaddam, Monatsh. Chem., 133, 1431 (2002): (j) I. Yavari and M. Bayat, Montsh. Chem., 134, 1221 (2003); (k) I. Yavari, M. Anari-Abbasinejad, and Z. Hossaini, Org. Biomol. Chem., 1, 560 (2003): (1) I. Yavari and A. Alizadeh, Synthesis, 237 (2004); I. Yavari, A. Alborzi, Sh. Dehghan, and F. Nourmohammadian, Phosphorus, Sulfur, and Silicon, 180, 625 (2005); (m) I. Yavari, F. Nasiri, and H. Djahaniani, Phosphorus, Sulfur, and Silicon, 180, 453 (2005); (n) I. Yavari, F. Nasiri and H. Djahaniani, Polish J. Chem., 78, 1871 (2004); (o) I. Yavari, M. Adib, Sh. Abdolmohammadi, and M. Aghazadeh, Monatsh. Chem., 134, 1093 (2003); (p) I. Yavari, M. Aghazadeh, and M. Tafazzoli, Phosphorus, Sulfur, and Silicon, 177, 1101 (2002); (q) I. Yavari and M. Bayat, Synthetic Commun., 32, 2527 (2002).
- [9] (a) A. W. Johnson, Ylides and Imines of Phosphorus (Wiley, New York, 1993); (b) L.
 D. Quin, A Guide to Organophosphorus Chemistry (Wiley, Interscience, New York, 2000).
- [10] (a) E. Zbiral, Synthesis, 775 (1975); (b) K. B. Becker, Tetrahedron, 36, 1717 (1980);
 (c) A. N. Hughes, Heterocyles, 15, 637 (1981) and references therein; (d) O. I. Kolodiazhnyi, Tetrahedron, 52, 1855 (1996); (e) O. I. Kolodiazhynyi, Russ. Chem. Rev., 66, 225 (1997).