ORGANIC LETTERS

2005
Vol. 7, No. 12
2469−2471

Efficient Synthesis and Environmentally Friendly Reactions of PEG-Supported 1,2-Diaza-1,3-butadiene

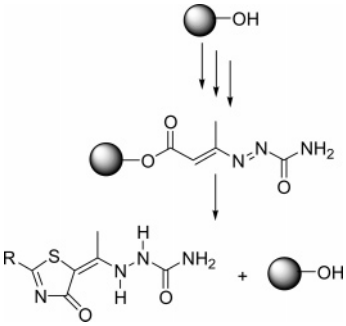
Orazio A. Attanasi, Lucia De Crescentini, Gianfranco Favi, Paolino Filippone,* Samuele Lillini, Fabio Mantellini,* and Stefania Santeusanio

Istituto di Chimica Organica della Facoltà di Scienze Matematiche, Fisiche e Naturali, Università degli Studi di Urbino "Carlo Bo", Via Sasso 75, 61029 Urbino, Italy

f.mantellini@uniurb.it

Received April 11, 2005

ABSTRACT



Here, we report the protocol for the preparation of new poly(ethylene glycol)-supported 1,2-diaza-1,3-butadiene. In addition, we discuss an application of this supported reagent in an efficient and environmentally friendly one-pot synthesis of 2-thiazol-4-one derivatives by reaction with thioamides.

Solid-phase organic synthesis has become increasingly important in the last 10 to 15 years, largely because of the emergence of combinatorial chemistry, which has enabled the parallel synthesis of libraries of compounds.[1] When designing a synthesis on solid support, one key consideration is selecting the linker through which the substrate is attached to the support, as well as the type of support. In consideration of their great interest, 1,2-diaza-1,3-butadienes have been intensively investigated by several authors.[2] We previously reported the protocol for preparing these compounds in the solid phase using poly(styrene) resins. The coupling sites were the ester group at position four[3] or the azo group[4] of the azo-ene system. The heterogeneous nature of these syntheses might result in some problems, such as difficulty in characterizing the insoluble polymer-supported compounds.

In recent years, however, polymer-supported liquid-phase synthesis has been studied intensely.[5] In fact, the advantages

* Fax: +390722303441.

(1) (a) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (b) Krchňak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61. (c) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607.

(2) (a) Figuereido, J. O.; Kascheres, C. *J. Org. Chem.* **1997**, *62*, 1164. (b) Caposcialli, N.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1998**, *54*, 786. (c) Schantl, J. R.; Nàdenik, P. *Synlett* **1998**, 786. (d) South, M. S. *J. Heterocycl. Chem.* **1999**, *36*, 301. (e) Banert, K. In *Targets in Heterocyclic Systems-Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2000; Vol. 3, p 1. (f) Polanc, S. In *Targets in Heterocyclic Systems-Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2000; Vol. 3, p 33. (g) Boeckman, R. K., Jr.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3647. (h) Boeckman, R. K., Jr.; Ge, P.; Reed, J. E. *Org. Lett.* **2001**, *3*, 3651. (i) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2261. (j) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2001**, *66*, 5139. (k) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2002**, *67*, 2241. (l) Alonso, C.; Palacios, F.; Rubiales, G.; Villegas, M. *Tetrahedron Lett.* **2004**, *45*, 4031. (m) Aparicio, D.; Yago, L.; Palacios, F.; de los Santos, J. M. *Tetrahedron* **2005**, *61*, 2815.

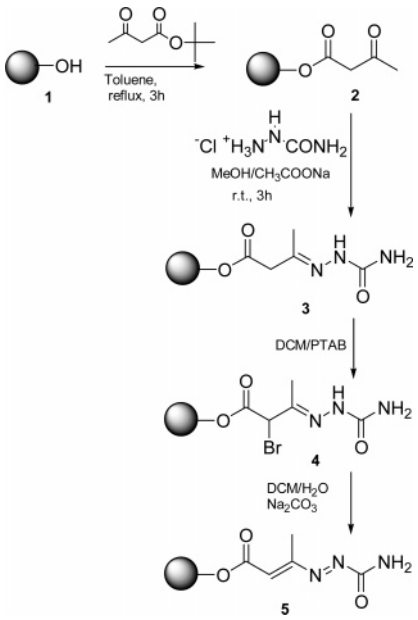
(3) (a) Attanasi, O. A.; Filippone, P.; Guidi, B.; Hippe, T.; Mantellini, F.; Tietze, L. F. *Tetrahedron Lett.* **1999**, *40*, 9277. (b) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Tietze, L. F. *Tetrahedron* **2001**, *57*, 5855.

10.1021/ol050775i CCC: $30.25
Published on Web 05/13/2005

of both homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, ease of analysis) and solid-phase methods (use of excess reagents and easy isolation and purification of products) coexist in this technique. Moreover, the soluble polymer-bound species permit the use of ^{1}H NMR spectroscopy to monitor the reaction process and to determine directly the structures of products attached to the polymer support. Among the various soluble polymers, poly(ethylene glycol) (PEG) is the most useful and promising.[6] Therefore, we decided to synthesize 1-aminocarbonyl 1,2-diaza-1,3-butadiene bound to PEG support and to perform preliminary tests of the preparation of some 2-thiazolin-4-ones previously obtained in solution.[7]

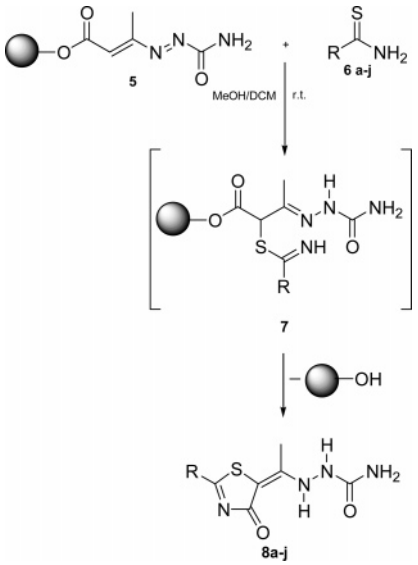
The polymer support (PEG methyl ether, MW 5000) was esterified by treatment with *tert*-butyl acetoacetate in toluene under reflux, in accordance with Witzeman's procedure.[8] The reaction progress was monitored by ^{1}H NMR analysis using $CDCl_3$ as the solvent. When the transesterification reaction was completed (3 h), the PEG-supported β-ketoester **2** was obtained by precipitation in diethyl ether (91% yield).[9,10] The separated solid was dissolved in methanol, and the reaction with semicarbazide hydrochloride in the presence of sodium carbonate led to PEG-supported hydrazone **3** (89% yield).[9,11] This latter compound was converted to the corresponding brominated hydrazone **4** by adding portionwise 1 equiv of phenyltrimethylammonium tribromide (PTAB) in dichloromethane (DCM) at room temperature.[12] The mixture was then treated directly with an aqueous saturated solution of sodium carbonate, which induces a conjugate elimination of hydrobromic acid with consequent formation of a new PEG-supported 1-aminocarbonyl 1,2-diaza-1,3-butadiene **5**, which was separated as solid (82% yield)[9,13] by addition of diethyl ether to the crude (Scheme 1).[14]

Scheme 1. Preparation of PEG-Supported 1-Aminocarbonyl 1,2-Diaza-1,3-butadiene



As shown in Scheme 2, the PEG-supported 1,2-diaza-1,3-butadiene **5** was treated with 4 equiv of variously substituted thioamides **6a**−**j**. The one-pot reactions were carried out at room temperature in a solution of dichloromethane/methanol (1:5) within 1.0−4.5 h to afford 2-thiazolin-4-ones **8a**−**j** that,

Scheme 2. Synthesis of 2-Thiazolin-4-ones **8a**−**j**



(4) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. *Synlett.* **2003**, 1183.

(5) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (b) Harwig, C. W.; Gravert, D. J.; Janda, K. D. *Chemtracts* **1999**, *12*, 1. (c) Wentworth, J.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (d) Bergbreiter, D. E. *Med. Res. Rev.* **1999**, *19*, 439. (e) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546. (f) Shang, Y.; Wang, Y. *Tetrahedron Lett.* **2001**, *43*, 2247.

(6) (a) Harris, J. M. *Poly (Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications*; Plenum Press: New York, 1992; Chapter 1. (b) Zhao, X.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433. (c) Blettner, C. G.; Konig, W. A.; Quthter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307. (d) Yeh, C. M.; Tung, C. L.; Sun, C. M. *J. Comb. Chem.* **2000**, *2*, 341. (e) Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932. (f) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem.—Eur. J.* **2000**, *6*, 133. (g) Fu, Y.; Etienne, M. A.; Hammer, R. P. *J. Org. Chem.* **2003**, *68*, 9854. (h) Wang, Y. G.; Lin, X. F.; Cui, S. L. *Synlett* **2004**, 1175. (i) Zhang, Z.; Pickens, J. C.; Hol, W. G. J.; Fan, E. *Org. Lett.* **2004**, *6*, 1377. (j) Chen, C.; Chen, Y. J. *Tetrahedron Lett.* **2004**, *45*, 113. (l) Chen, Z.; Yue, G.; Lu, C.; Yang, G. *Synlett* **2004**, 1231.

(7) (a) Attanasi, O. A.; De Crescentini, L.; Foresti, E.; Galarini, R.; Santeusanio, S.; Serra-Zanetti, F. *Synthesis* **1995**, 1397. (b) Arcadi, A.; Attanasi, O. A.; De Crescentini, L.; Guidi, B.; Rossi, E.; Santeusanio, S. *Gazz. Chim. Ital.* **1996**, *127*, 609.

(8) Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713.

(9) The yields of the PEG-supported compounds were determined by weight with the assumption that M_W is 5000 Da for the PEG fragment. The M_W actually ranged from 4500 to 5500. The indicated yields were for pure compounds. The purity of these compounds was determined by ^{1}H NMR analysis in $CDCl_3$ at 400 MHz with presaturation of the methylene signals of the polymer at $\delta = 3.63$ ppm. In recording the NMR spectra, a relaxation time of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integrations. The relaxation delay was selected after T_1 measurements. The integrations of the PEG CH_2OCH_3 fragment at $\delta = 3.30$ and $\delta = 3.36$ were used as internal standard. The estimated integrations error was ±5%.

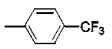
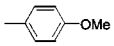
(10) For the PEG-bound β-ketoester **2**, the diagnostic signal was the singlet of the methyl group that resonates at $\delta = 1.54$ ppm.

(11) For the PEG-supported hydrazone **3**, the diagnostic signal was the singlet of the methyl group that resonates at $\delta = 1.99$ ppm.

(12) (a) Visweswariah, S.; Prakash, G.; Bhushan, V.; Chandrasekaran, S. *Synthesis* **1982**, 309. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Serra-Zanetti, F. *J. Heterocycl. Chem.* **1985**, *22*, 1341. (c) Attanasi, O. A.; Filippone, P.; Guerra, P.; Serra-Zanetti, F. *Synth. Commun.* **1987**, *17*, 555.

with the exception of **8a**,**g**,[7a] were synthesized for the first time. These latter compounds were released into the reaction medium from which they directly precipitated as pure products (for yields, purity, and reaction times, see Table 1).[15,16] The mechanism implicates the first SH nucleophilic attack of the thioloimido function to the terminal carbon atom of the azo-ene system. The subsequent intramolecular NH nucleophilic attack onto the ester group of the hydrazonic intermediate **7** leads to the thiazolinone ring closure, with loss of PEG−OH.

Table 1. Yields,[a] Purity, and Reaction Times for the Synthesis of 2-Thiazolin-4-ones **8 a**−**j**

6	8	R	yield (%)	purity (%)	reaction time (h)
a	**a**		49	99	1.0
b	**b**		31	95	4.5
c	**c**		48	91	2.0
d	**d**		51	97	2.5
e	**e**		48	98	2.5
f	**f**		34	91	2.5
g	**g**		59	93	3.0
h	**h**		70	96	1.5
i	**i**		57	94	1.5
j	**j**		41	99	1.0

[a] The yield of the pure isolated products **8a**−**j** are based on reagent **5** and were determined by weight with the assumption that M_W is 5000 Da for the PEG fragment. The M_W actually ranged from 4500 to 5500.

In the previous liquid-phase synthesis of the same thiazolin-4-ones,[7] we observed the formation of both hydrazono and hydrazino tautomeric forms. Surprisingly, the procedure with PEG-bound 1,2-diaza-1,3-butadiene described here permits us to obtain thiazolin-4-ones exclusively in the hydrazino-isomer with *E* configuration.

In conclusion, this paper reports an inexpensive strategy for synthesizing a new PEG-supported 1,2-diaza-1,3-butadiene; its use in a simple and environmentally friendly one-pot reaction with thioamides to obtain 2-thiazol-4-ones is also described. All the reactions are highly efficient in yielding the desired compounds at room temperature and require only simple workup procedures. Crude products are usually obtained in high purity and high yield by simple precipitation and washing, without further purification. In addition, this technique is highly selective, as it allows us to obtain 2-thiazol-4-ones only in the *E*-hydrazino isomeric form.

Acknowledgment. This work was supported by the financial assistance from the Ministero dell'Università, dell'Istruzione e della Ricerca (MIUR)-Roma and Università degli Studi di Urbino.

Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via Internet at http://pubs.acs.org.

OL050775I

(13) For the 1-aminocarbonyl 1,2-diaza-1,3-butadiene **5**, the diagnostic signal was the singlet of the methyl group that resonates at $\delta = 2.30$ ppm.

(14) **Procedure for the Synthesis of PEG-Supported 1-Aminocarbonyl 1,2-Diaza-1,3-butadiene 5.** Poly(ethylene glycol)methyl ether (average MW 5000) **1** (5.00 g) in toluene (40 mL) was refluxed for 3 h in the presence of *tert*-butyl acetoacetate (10 equiv). After completion of the raction, diethyl ether (60 mL) was added to the mixture to allow the precipitation of the PEG-bound β-ketoester **2**, which was collected by filtration and washed three times with diethyl ether (20 mL). This latter compund **2** was treated with semicarbazide hydrochloride (5 equiv) and sodium carbonate (5 equiv) in methanol (50 mL). The reaction mixture was allowed to stand at room temperature for 5 h to obtain PEG-supported hydrazone **3**. The reaction solvent was evaporated under reduced pressure; the crude was dissolved in dichloromethane (180 mL) and washed with water. The organic layer was dried on sodium sulfate and PTAB was added portionwise under magnetic stirring in 1.5 h to obtain polymer-bound α-bromohydrazone **4**. Then, the mixture was treated with an aqueous saturated solution of sodium carbonate (30 mL × 2), and the organic layer was dried on sodium sulfate. Dichloromethane was evaporated under reduced pressure, and the final 1-aminocarbonyl 1,2-diaza-1,3-butadiene **5** was precipitated with diethyl ether (40 mL), filtered, and washed with diethyl ether (20 mL × 3).

(15) **General Procedure for the Synthesis of 2-Thiazolin-4-ones 8a**−**j.** To a stirred solution of PEG-supported 1-aminocarbonyl 1,2-diaza-1,3-butadiene (5.00 g) in dichloromethane/methanol (1:4) (8 mL) was added a solution of thioamides (3 equiv) in methanol (2 mL). After 1.0−4.5 h, the typical red color of 1,2-diaza-1,3-butadiene disappeared, and a precipitate appeared. The TLC check revealed the presence of a spot corresponding to the final 2-thiazolin-4-ones **8a**−**j** that were collected by filtration in satisfactory purity.

(16) **Analytical Data of Compound 8d.** Yellow solid, mp 200−201 °C. IR (Nujol) ν_{max} 3313, 3147, 1712, 1661 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 2.27 (s, 3H), 6.22 (brs, 2H), 7.55 (d, 2H, $J = 7.6$ Hz), 7.88 (d, 2H, $J = 7.6$ Hz), 9.27 (s, 1H), 11.65 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 15.1 (q), 108.8 (s), 127.9 (d), 130.0 (d), 132.3 (s), 135.8 (s), 143.8 (s), 157.4 (s), 161.2 (s), 162.3 (s). MS (EI) *m*/*z* 312 [M$^+$ + 2] (1), 310 [M$^+$] (4), 295 (3), 293 (10), 139 (30), 137 (100).