Pergamon

Tetrahedron Letters 41 (2000) 691–695

TETRAHEDRON LETTERS

Generation and cycloaddition of polymer-supported azomethine imines: traceless synthesis of pyrazole derivatives from α-silylnitrosoamide derivatives bound to resin

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Received 5 October 1999; accepted 8 November 1999

Abstract

1,3-Dipolar cycloaddition of polymer-supported azomethine imines with dimethyl acetylenedicarboxylate (DMAD) gave pyrazole derivatives in good yields. The azomethine imines were generated from polymer-supported α-silylnitrosoamides by a 1,4-silatropic shift. The feature of this reaction is that no cleavage operations are required after the cycloaddition.

Solid-phase organic synthesis (SPOS)[1] is currently an important technique, because of the progress in combinatorial chemistry and high-throughput screening.[2] One of the most useful methods for the synthesis of diverse heterocyclic compounds is 1,3-dipolar cycloaddition,[3] and, in the past few years, a considerable number of solid-phase syntheses of heterocycles using 1,3-dipolar cycloaddition have been reported.[4]

In the course of our studies of the generation of 1,3-dipoles from α-silylimines,[5] α-silylamides,[6] or α-silylnitrosamines[7] which involve an intramolecular silatropic shift, we found that a similar cycloaddition can be performed by means of α-silylnitrosoamides and dipolarophiles to give *N*-unsubstituted pyrazoles in excellent yields (Scheme 1).[7] Thus, azomethine imine **2**, which is generated via a 1,4-silatropic shift of the silyl group onto the oxygen of the nitroso group, undergoes a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to give the five-membered ring adduct **3**. It is interesting that the acyl group is spontaneously eliminated as a silylester from **3** and *N*-unsubstituted pyrazole **4** is obtained after aromatization. If a polymer is attached to the acyl group of **1**, this would greatly enhance the versatility of the reaction. Namely, the target pyrazole could be separated from the polymer-supported silylester by simply filtering the reaction mixture. In this paper, we describe such an approach, namely, the traceless synthesis of pyrazole derivatives from polymer-supported α-silylnitrosoamides.

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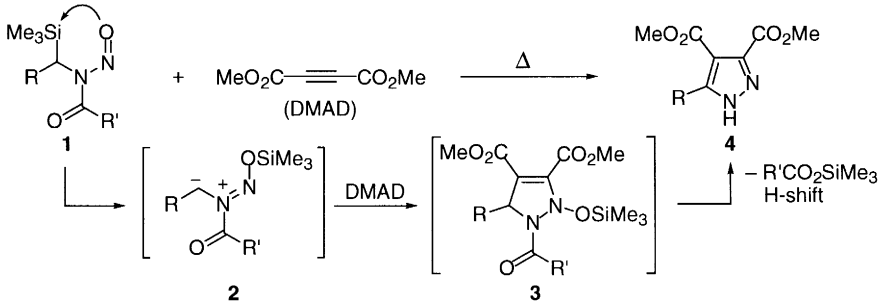
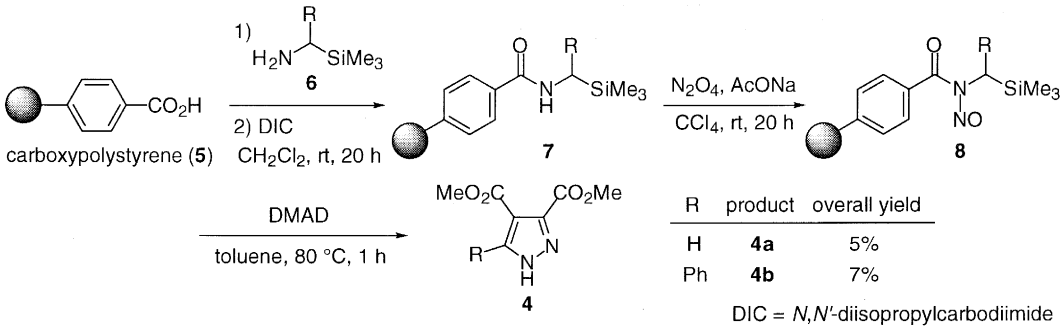
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02140-1



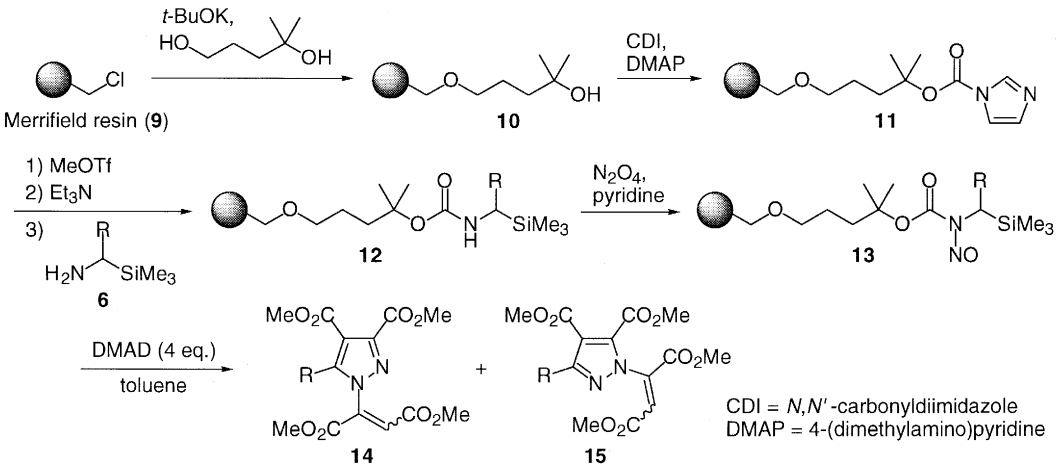
Scheme 1.

We initially examined the preparation of a polymer-supported α-silylnitrosoamide **8** according to Scheme 2. The α-silylamine **6** was coupled with carboxypolystyrene **5** in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) in dichloromethane to give a polymer-supported α-trimethylsilylamide **7**. Treatment of resin **7** with dinitrogen tetroxide in carbon tetrachloride resulted in the complete conversion into **8**, which could be verified by the change in IR spectra of the carbonyl function. Cycloadditions of the generated **8** with DMAD (2 equiv.) were performed at 80°C for a period of 1 h. Although both resins (**8a** and **8b**), which were prepared from trimethylsilylmethylamine (**6a**) and α-(trimethylsilyl)benzylamine (**6b**), afforded the corresponding pyrazoles (**4a** and **4b**), the yields were low. Increasing the reaction time or elevating the temperature failed to improve the yields. One reason for the poor efficiency of the cycloaddition might be due to the short distance between the polymer-support and the azomethine imine unit. Another might be that a rate of the side reaction caused by the intramolecular acyl shift onto the nitroso group (Huisgen–White rearrangement[8]) was much greater than that of the desired cycloaddition.



Scheme 2.

A preliminary solution-phase experiment revealed that the cycloaddition of *tert*-butyl α-silylnitrosocarbamate with DMAD does not afford a side reaction product. This may be because of the higher electron density on the carbon of the carbamate than that of the nitrosoamide. With this fact in mind, we next designed a polymer-supported α-silylnitrosocarbamate **13** which contains an extended linker (Scheme 3). Of the methods available for the synthesis of polymer-supported carbamates,[9] we selected and synthesized the imidazole-modified resin **11**, reported by Hernández and Hodges,[9c] as an alkoxycarbonylating reagent. Activation of **11** with methyl trifluoromethanesulfonate (MeOTf),[9c] followed by treatment with α-silylamine **6** gave a polymer-supported carbamate **12**. Nitrosation of **12** was performed with dinitrogen tetroxide to afford **13**. The progress of the reaction was monitored directly by FT-IR and ^{1}H MAS (magic angle spinning) NMR[10] without cleavage of the resins (Fig. 1a,b).



Scheme 3.

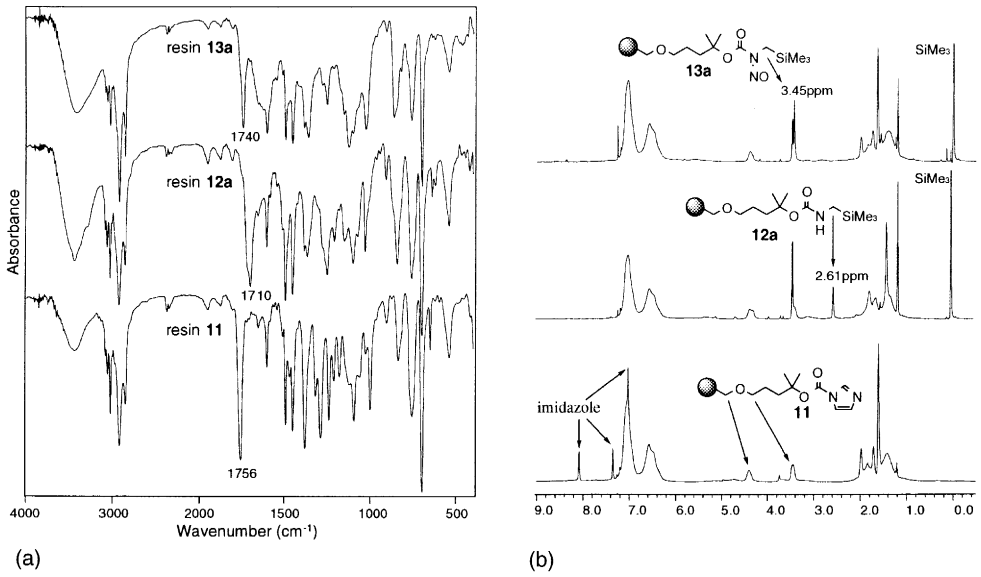


Fig. 1. (a) FT-IR spectra of resins **11**, **12a**, and **13a**; (b) 600 MHz ^{1}H MAS NMR spectra of resins **11**, **12a**, and **13a** (in the Nano NMR probes)

The prepared polymer-supported α-silylnitrosocarbamate **13** was reacted with DMAD in toluene under several sets of conditions (Table 1). After the reaction, the polymer was filtered off and the filtrate was purified by silica gel chromatography.[11] The yield was determined, based on the initial loading of the Merrifield resin. The reaction rate using **13** was slow compared to that using resin **8** and, in the case of an extended reaction time, the anticipated *N*-unsubstituted pyrazole reacted with an excess of DMAD to give Michael adducts **14** and **15**.[12] When **13a** was reacted at 80°C for 2 h, pyrazole **14a** was obtained in 26% yield (entry 1). Furthermore, an increase of the reaction time was effective in increasing the yield of **14a** and the optimum yield (70%) was achieved after 48 h (entry 3). Elevation of temperature to 110°C did not result in an improvement, though the yields were almost the same as those of the reactions at 80°C (entries 4 and 5). On the other hand, cycloaddition of phenyl-substituted α-silylnitrosocarbamate **13b** was performed using the optimized conditions to give two types of Michael adducts **14b** and **15b**

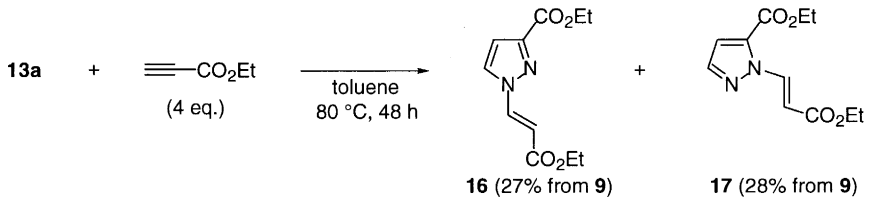
Table 1
Cycloaddition of resin **13** with DMAD (4 equiv.)

entry	α-silylnitrosocarbamate	R	*T* (°C)	time (h)	products (yield, %) [a]
1	**13a**	H	80	2	**14a** (26)
2	**13a**	H	80	24	**14a** (59)
3	**13a**	H	80	48	**14a** (70)
4	**13a**	H	110	24	**14a** (50)
5	**13a**	H	110	48	**14a** (64)
6	**13b**	Ph	80	48	**14b** (26) + **15b** (21)
7	**13c**	4-methoxyphenyl	80	48	**14c** (12) + **15c** (11)
8	**13d**	4-fluorophenyl	80	48	**14d** (21) + **15d** (21)

[a] Isolated yield. The yield was determined based on the initial loading of Merrifield resin .

in moderate yield (entry 6). The formation of **15b** may be because of the steric hindrance of the phenyl group. Similar cycloadducts were obtained from the reactions of 4-methoxyphenyl- or 4-fluorophenyl-substituted α-silylnitrosocarbamates **13c** or **13d** (entries 7 and 8).

The reaction of **13a** with ethyl propiolate was also examined. In this case, the initially formed *N*-unsubstituted pyrazole was regioselectively one product, the 3-substituted pyrazole, which reacted with an excess of ethyl propiolate to give a mixture of **16** and **17** in good yield (Eq. (1)).



16 (27% from **9**) **17** (28% from **9**) (1)

In conclusion, we report the development of a novel synthesis of pyrazole derivatives using polymer-supported α-silylnitrosoamide derivatives. Intramolecular 1,4-silatropic shift of the α-silylnitrosoamide gave the polymer-supported azomethine imine which underwent 1,3-dipolar cycloaddition with the dipolarophile. Modification of the linker led to higher yields of products. It is noteworthy that the products can be easily separated from the polymer without any cleavage operation. We are currently applying this method to the synthesis of diverse pyrazole derivatives from several resins and dipolarophiles.

Acknowledgements

This work was supported, in part, by Special Coordination Funds from the Science and Technology Agency of the Japanese Government and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. We also acknowledge the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining 600 MHz ^{1}H MAS NMR spectra.

References

1. (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999,** *99,* 1549. (b) Bunin, B. A. In *The Combinatorial Index*; Academic Press: San Diego, 1998.
2. (a) Obrecht, D.; Villalgordo, J. M. In *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon: Oxford, 1998. (b) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C.

Angew. Chem., Int. Ed. Engl. **1996**, *35*, 2288. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (d) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (e) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.

3. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, pp. 1–176.
4. (a) Park, K.-H.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 5841. (b) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081. (c) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800. (d) Haap, W. J.; Kaiser, D.; Walk, T. B.; Jung, G. *Tetrahedron* **1998**, *54*, 3705. (e) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211. (f) Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. *Tetrahedron Lett.* **1998**, *39*, 2447. (g) Cheng, J.-F.; Mjalli, A. M. M. *Tetrahedron Lett.* **1998**, *39*, 939. (h) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Löwe, R. S.; Austin, D. J. *Bioorg. Med. Chem.* **1998**, *6*, 1273. (i) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett.* **1997**, *38*, 7139. (j) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973. (k) Kurth, M. J.; Randall, L. A. A.; Takenouchi, K. *J. Org. Chem.* **1996**, *61*, 8755. (l) Hollinshead, S. P. *Tetrahedron Lett.* **1996**, *37*, 9157. (m) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671. (n) Mjalli, A. M. M.; Sarshar, S.; Baiga, T. J. *Tetrahedron Lett.* **1996**, *37*, 2943. (o) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029. (p) Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4204.
5. (a) Komatsu, M.; Ohno, M.; Tsuno, S.; Ohshiro, Y. *Chem. Lett.* **1990**, 575. (b) Iyoda, M.; Sultana, F.; Komatsu, M. *Chem. Lett.* **1995**, 1133.
6. Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813.
7. Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 8849.
8. (a) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6008. (b) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6011. (c) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6014. (d) White, E. H.; Woodcock, D. J. In *The Chemistry of Amino Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1968; Chapter 8, pp. 440–459. (e) Bieron, J. F.; Dinan, F. J. In *The Chemistry of Amides*; Patai, S., Ed.; John Wiley & Sons: New York, 1970; Chapter 4, pp. 255–262.
9. (a) Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589. (b) Rotella, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 12246. (c) Hernández, A. S.; Hodges, J. C. *J. Org. Chem.* **1997**, *62*, 3153.
10. (a) Luo, Y.; Ouyang, X.; Armstrong, W.; Murphy, M. M. *J. Org. Chem.* **1998**, *63*, 8719. (b) Chin, J.; Fell, B.; Shapiro, M. J.; Tomesch, J.; Wareing, J. R.; Bray, A. M. *J. Org. Chem.* **1997**, *62*, 538. (c) Wehler, T.; Westman, J. *Tetrahedron Lett.* **1996**, *37*, 4771.
11. Typical procedures: To a mixture of resin **12** (986 mg, 1.07 mmol) and pyridine (343 μL, 4.28 mmol) in CCl_4 (10 mL), a solution of dinitrogen tetroxide in CCl_4 (0.46 M, 4.65 mL, 2.14 mmol) was added dropwise at room temperature and the mixture was shaken at the same temperature for 1 h. The reaction mixture was filtered and washed sequentially with CCl_4 (10 mL×1), THF (10 mL×3), THF:H_2O (1:1, 10 mL×3), H_2O (10 mL×3), THF:H_2O (1:1, 10 mL×3), THF (10 mL×3), and Et_2O (10 mL×1) and dried in vacuo to give resin **13** (1.08 g). To a suspension of resin **13** (326 mg, 0.324 mmol) in toluene (3.2 mL) was added DMAD (160 μL, 1.30 mmol) and the mixture was then stirred at 110°C for 48 h. The reaction mixture was filtered and washed with toluene (10 mL×3). The filtrate was concentrated in vacuo and the residue was chromatographed on 10 g of silica gel (eluent: hexane:AcOEt=9:1 then 2:1) to give pyrazole (*E*)-**14** (32.1 mg, 30%) and (*Z*)-**14** (36.0 mg, 34%). The structure of (*E*)-**14** was determined by spectral analysis and X-ray crystal structure determination.
12. Similar Michael additions of cycloadducts with excess of acetylenic dipolarophiles are well-known. For example, see: Saikachi, H.; Kitagawa, T.; Sasaki, H. *Chem. Pharm. Bull.* **1979**, *27*, 2857.