HETEROCYCLES, Vol. 56, 2002, pp. 369 - 377, Received, 18th June, 2001

NEW SOLID-SUPPORTED REAGENTS (SSRs) FOR SELECTIVE ACYLATION OF AMINES

Maurizio Botta,* Federico Corelli,* Elena Petricci and Catia Seri¶

Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena
A. Moro - 53100 Siena, Italy

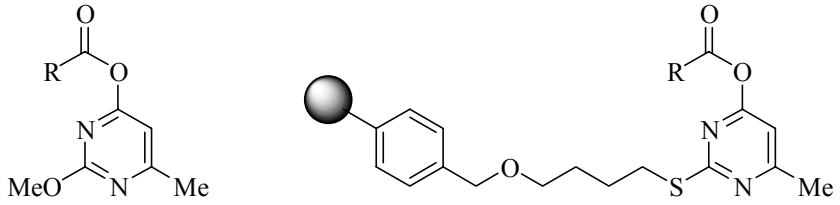
Abstract – The pyrimidine linker (**4**) was prepared by solid phase synthesis starting from Merrifield resin. Acylation of **4** with different acyl chlorides gave polymer-bound 4-acyloxypyrimidines (**2a-c**), which proved to be useful solid-supported reagents for the selective acylation of amines. Their use in solution combinatorial chemistry has been also envisaged.

Recent reports indicate increasing efforts toward high throughput solution synthesis using solid-supported reagents (SSRs).[1-4] Used since 1960, SSRs have been the subject of several review articles.[5] After the development of combinatorial synthesis, the use of SSRs became attractive and suitable for parallel synthesis because their reactions are often very clean, high-yielding, and easily monitored by TLC. Moreover, isolation of the reaction product simply involves filtration of the resin and evaporation of the solvent.

The definition of SSRs encompasses reagents that are either covalently or ionically bound to the support. SSRs can serve a variety of purposes: stoichiometric reagents that participate in the reaction,[6-8] reaction catalysts,[9-12] protecting groups that allow for selective transformation on another portion of the molecule,[2,9] or scavenger that help in the removal of impurities.[1, 13-17]

In a previous note, we reported a high-yielding solution phase synthesis of 4-*O*-acylated pyrimidines (**1**) (Chart 1), active as antitumor, antimicrobial and antiviral agents, and able to acylate amines, phenols and thiophenols.[18] We have envisaged the possible development of similar, polymer-bound reagents (**2**), and report herein the preparation of these new SSRs as well as their use for the selective acylation of amines.

The rapid development of combinatorial synthesis prompted us to adopt these SSRs for the synthesis of amides, since the amide bond is present in a large number of pharmacologically active compounds.

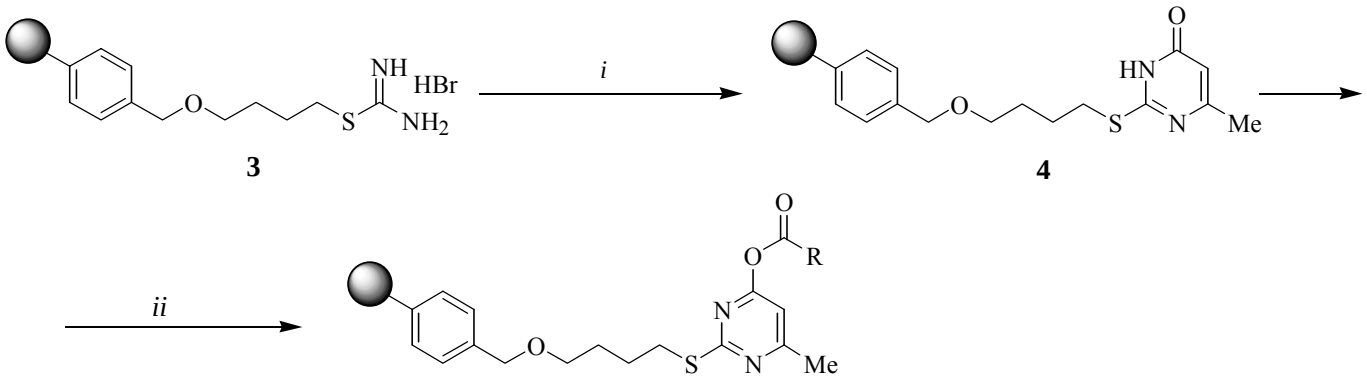


1 **2**

Chart 1

The synthesis of SSRs (**2**) is depicted in Scheme 1. As the starting material we chose the isothiouronium salt (**3**), prepared according to the literature,[19] in which the isothiourea moiety is linked to the solid support (Merrifield resin) by a tetramethylene spacer that is expected to create a "chemical distance" from the polymer and to give more "solution like" properties and better solvent compatibility to the resin, thus tailoring the swelling properties of the material. The condensation reaction of **3** with ethyl acetoacetate was best performed in a water/ethanol (1 : 1) mixture, in the presence of calcium hydroxide as a mild base.

Scheme 1



3 **4**

2a-c

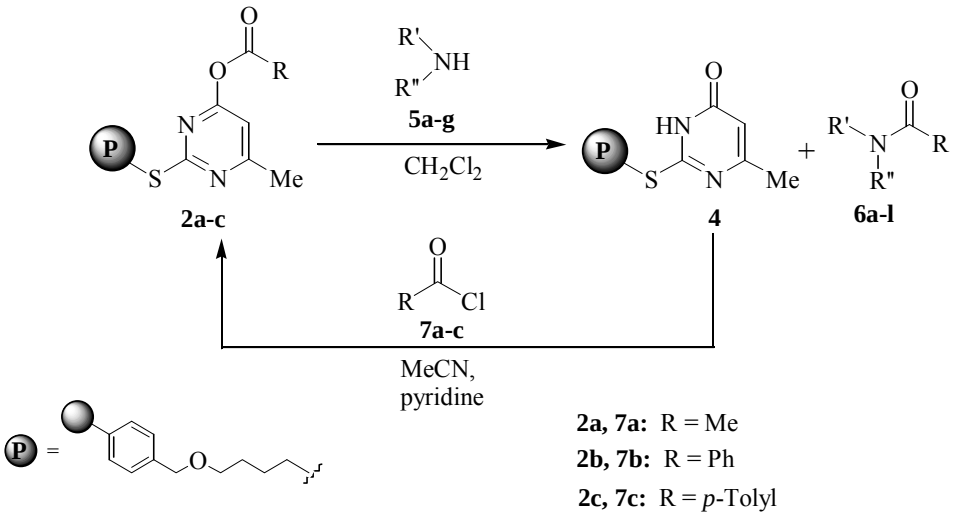
a: R = Me; **b:** R = Ph; **c:** R = *p* - Tolyl

i. Ethyl acetoacetate, H_2O/EtOH (1:1), $Ca(OH)_2$; *ii.* **7a-c**, pirydine, MeCN.

In order to drive the reaction to completion, the condensation reaction was carried out twice under the same experimental conditions. The pyrimidinone derivative (**4**) so obtained was treated with the appropriate acyl chloride at room temperature for 24 h to give regioselectively the polymer-bound 4-acyloxypyrimidines (**2a-c**). Although this procedure requires the use of excess reagents in all of the steps, yet it is fast and convenient since neither solution steps nor purifications of intermediates are needed.

The SSRs (**2a-c**) reacted smoothly with amines (**5a-g**) in dichloromethane solution at room temperature (Scheme 2, Table 1); after filtration of the resin (**4**) and evaporation of the solvent, amides (**6a-l**) were obtained as pure crystalline solid in good yield (65-98%). The resin (**4**) could be recycled and transformed again into the acylating SSR (**2a-c**) for at least three times with no decrease in the reaction yield.

Scheme 2



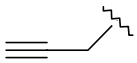
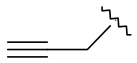
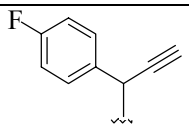
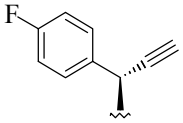
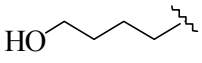
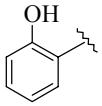
for R', R" in compounds (**5**) and (**6**), see Table 1

The loading of the resin was experimentally determined to be 68% by treating **2a** with a known excess of amine (**5a**) and weighing the amount of unreacted **5a** at the end of the acylation reaction.

The SSRs (**2a-c**) proved to be able to transfer efficiently either aliphatic (**2a**) or aromatic (**2b**,**c**) acyl groups to primary and secondary amines (aliphatic and aromatic), without racemization in the case of enantiomerically pure amines, such as **5f**.[20] Furthermore, these new reagents showed the capability of acylating selectively the amino group even when other nucleophilic (alcohol or phenol) functionalities are present in the same molecule (**5g,h**). Finally, these SSRs showed potential for the combinatorial synthesis of amide libraries in solution phase. In fact, when **2b** was reacted simultaneously for 24 h with amines

(**5a,b,l**), benzamides (**6a,b,l**) were obtained in 50% overall yield and in the ratio 3.3 : 1.6 : 10, as determined by GC-MS analysis.

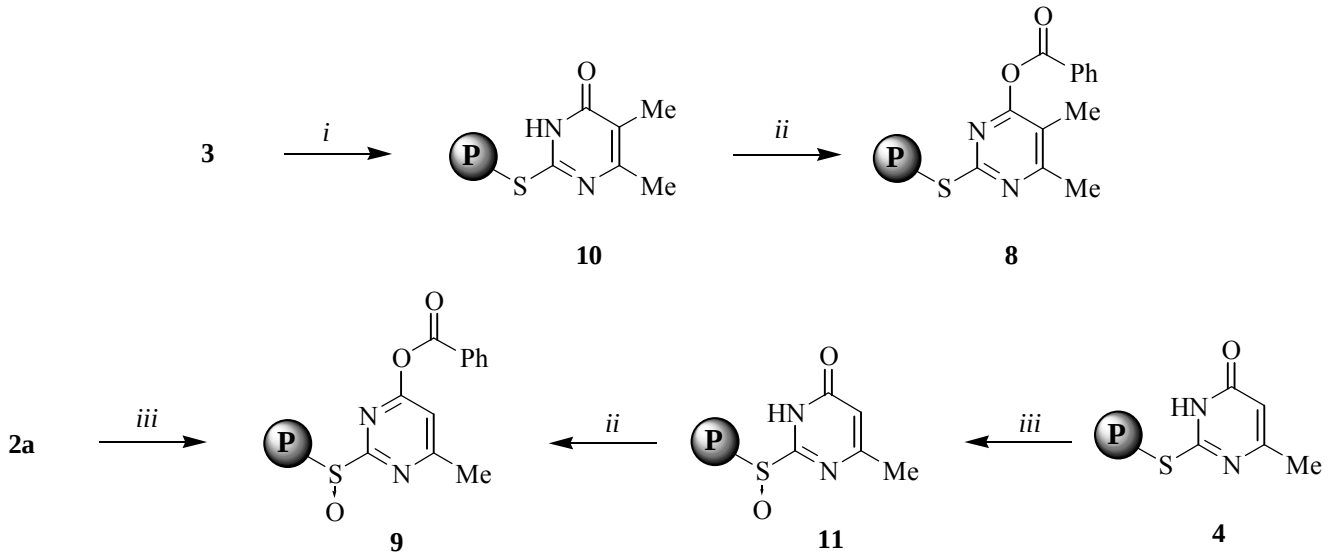
Table 1

Compd	R	R'	R''	Yield (%)
6a	Ph	H	Bn	**85**
6b	Ph	H		**92**
6c	Me	H	Bn	**90**
6d	Me	H		**74**
6e	Me	H		**87**
6f	Me	H		**89**
6g	Ph	H		**82**
6h	Ph	H		**65**
6i	*p* - Tolyl	H	Bn	**80**
6l	Ph			**98**

With the aim to explore the dependence of acylating ability of these SSRs on their electronic properties, two new reagents (**8**) and (**9**) (Scheme 3), bearing an electron donating and an electron withdrawing substituent, respectively, on the pyrimidine ring, were also synthesized. Compound (**8**) was prepared by condensation of **3** with ethyl 2-methyl acetoacetate, under the same experimental conditions used for the preparation of **4**, to give the pyrimidinone (**10**), which was then reacted with benzoyl chloride to afford the SSR (**8**). Sulfoxide (**9**) was best obtained by oxidation of **2b** with oxone.[20] An alternative procedure entailing first oxidation of **4** followed by acylation of the intermediate 2-sulfinylpyrimidinone (**11**) proved to be less convenient, due to the poorer reactivity of **11** towards oxone with respect to **2b**. Rather surprisingly, neither **8** or **9** showed better acylating properties than **2b**: in fact, when reacted with

benzylamine by stopping the reaction after 24 h, they gave the corresponding amide (**6a**) in only 35 and 40% yield, respectively, wheras **2b** gave **6a** in 54% yield, thus to be the faster acylation reagent.

Scheme 3



i. Ethyl 2-methylacetoacetate, H_2O/EtOH, $Ca(OH)_2$; *ii.* PhCOCl, pirydine, MeCN; *iii.* oxone, H_2O/MeOH.

In conclusion, we have developed new solid-supported reagents showing better performances in comparison with the usual reagents developed so far[2]; they possess in fact the following interesting properties: they are efficient and selective acylating reagents for amines; they are cheap and easily prepared by solid-phase synthesis; they show potential for the solution-phase combinatorial synthesis of amides; the by-product of the acylation reaction, *i. e.* the polymer-bound pyrimidinone (**4**), can be recycled for several reaction runs.

EXPERIMENTAL

General methods. Unless otherwise stated, all reactions were carried out under an argon atmosphere. Reagents were obtained from commercial suppliers and used without further purifications. Melting points are uncorrected. ^{1}H NMR spectra were measured at 200 MHz. Chemical shifts are reported relative to $CDCl_3$ at 7.24 ppm and tetramethylsilane at 0.00 ppm. FT-IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. EI low-resolution MS spectra were recorded with an electron beam of 70 eV.

The elementary analysis were obtained from a Perkin-Elmer 1600 Elemental Analyzer 240L.

Solid-supported Pyrimidinone (4). The polymer-bound isothiouronium salt (**3**) (4 g, 4 mmol of functional group) was suspended in a water (95 mL)/ethanol (95 mL) mixture and swollen for 10 min. $Ca(OH)_2$ (326 mg, 4.4 mmol) and 10 mL of ethyl acetoacetate was added (78 mmol). The reaction was stirred at rt for 72 h. After 24 h the pH was checked and kept alkaline by addition of $Ca(OH)_2$ (326 mg, 4.4 mmol). 20 mL of ethyl acetoacetate was added and the mixture was stirred at rt. After 48 h 10 mLs of ethyl acetoacetate were added. 72 h later the resin was filtered, washed successively with warm water (5 x 30 mL), ethanol (3 x 30 mL), dichlorometane (3 x 30 mL) and ether (3 x 30 mL). The reaction and the work-up were repeated once again on the resin and then this was dried at 25 °C for 4 h.

SSR (2a-c): general procedure. The solid-supported pyrimidinone (**4**) (500 mg, 0.5 mmol) was suspended in dry acetonitrile (15 mL) and swollen for 10 min. Dry pyridine (243 μL, 3 mmol) and 2 mmol of **7a-c** was added. The mixture was stirred at rt for 48 h. The resin was filtered, washed successively with dichloromethane (3 x 10 mL), toluene (3 x 10 mL) and dried *in vacuo* at 25 °C for 4 h.

2a: IR (nujol) 1744 (-O-**C=O**), 1232 (-**O-C**=O), 1149 (-**C-O**-C=O) cm^{-1}.

2b: IR (nujol) 1774(-O-**C=O**), 1269 (-**O-C**=O), 1145 (-**C-O**-C=O) cm^{-1}.

2c: IR (nujol) 1739(-O-**C=O**), 1234 (-**O-C**=O), 1150 (-**C-O**-C=O) cm^{-1}.

Amides (6a-l): general procedure. The solid supported reagent (**2a-c**) (500 mg, 0.34 mmol of functional group) was suspended in a dry dichloromethane solution and swollen for 10 min. The amine (**5a-g**) (0.34 mmol) was added to the mixture and the reaction was stirred at rt for 48 h. The resin was filtered, washed with dichlorometane and dried *in vacuo* at 25 °C for 4 h. The dichlorometane solution was evaporated and the amides (**6a-l**) was obtained in high yield.

6a: $C_{14}H_{13}NO$: calculated C 79.59, H 6.20, N 6.63; found C 79.63, H 6.37, N 6.82; mp 106-108 °C [lit.,[21] mp 106-107 °C]; ^{1}H-NMR ($CDCl_3$) δ 4.60-4.62 (d, 2H, *J* = 5.8 Hz), 6.65 (s, 1H), 7.32-7.41 (m, 5H), 7.75-7.79 (m, 5H).

6b: $C_{10}H_9NO$: calculated C 75.45, H 5.70, N 8.80; found C 75.36, H 5.62, N 8.69; mp 112-113 °C [lit.,[22] mp 112-113 °C]; ^{1}H-NMR ($CDCl_3$) δ 2.25-2.29 (t, 1H, *J* = 2.2 Hz); 4.20-4.24 (d, 2H, *J* = 1.9 Hz); 6.59 (s, 1H), 7.35-7.47 (m, 3H), 7.75-7.78 (d, 2H, *J* = 7.1 Hz).

6c: $C_9H_{11}NO$: calculated C 72.46, H 7.43, N 9.39; found C 72.50, H 7.53, N 9.47; mp 64-65 °C [lit.,[23] mp 64-65 °C]; ^{1}H-NMR ($CDCl_3$) δ 1.98 (s, 3H), 4.38-4.41 (d, 2H, *J* = 4.4 Hz), 5.80 (s, 1H), 7.16-7.34 (m, 5H).

6d: C_5H_7NO: calculated C 61.84, H 7.27, N 14.42; found C 61.93, H 7.33, N 14.53; mp 86.5-87.5 °C

[lit.,[24] mp 86.5-87.5 °C]; ^{1}H-NMR ($CDCl_3$) δ 1.98 (s, 3H), 2.18-2.21 (t, 1H, *J* = 2.2 Hz), 4.00-4.04 (m, 2H, *J* = 2.1 Hz), 5.65 (s, 1H).

6e: $C_{11}H_{10}NOF$: calculated C 69.10, H 5.27, N 7.33; found C 69.23, H 5.31, N 7.53; mp 116-118 °C [lit.,[25] mp 116-118 °C]; ^{1}H-NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.46-2.47 (d, 1H, *J* = 1.9 Hz), 5.93-5.98 (dd, 1H, J_1 = 1.5 Hz, J_2 = 6.5 Hz), 6.13 (s, 1H), 7.00-7.04 (m, 2H, *J* = 8.7 Hz), 7.42-7.48 (m, 2H, *J* = 5.3 Hz).

6f: $C_{11}H_{10}NOF$: calculated C 69.10, H 5.27, N 7.33; found C 69.23, H 5.31, N 7.53; mp 116-118 °C [lit.,[25] mp 116-118 °C]; ^{1}H-NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.46-2.47 (d, 1H, *J* = 1.9 Hz), 5.93-5.98 (dd, 1H, J_1 = 1.5 Hz, J_2 = 6.5 Hz), 6.13 (s, 1H), 7.00-7.04 (m, 2H, *J* = 8.7 Hz), 7.42-7.48 (m, 2H, *J* = 5.3 Hz); $[\alpha]_D^{25}$ + 51.27 ° (*c* = 1.12, $CHCl_3$) [lit.,[25] + 51.27 ° (*c* = 1.12, $CHCl_3$)].

6g: $C_{11}H_{15}NO_2$: calculated C 68.37, H 7.82, N 7.25; found C 68.24, H 7.91, N 7.06; mp 71-73 °C [lit.,[26] mp 71-73 °C]; ^{1}H-NMR ($CDCl_3$) δ 1.55-1.75 (m, 4H, *J* = 2.9 Hz), 2.66 (s, 1H), 3.38-3.48 (q, 2H, *J* = 6.6 Hz), 3.62-3.68 (t, 2H, *J* = 5.2 Hz), 6.79 (s, 1H), 7.30-7.47 (m, 3H, *J* = 2.5 Hz), 7.71-7.76 (dd, 2H, J_1 = 1.8 Hz, J_2 = 6.3 Hz); IR ($CHCl_3$) ν 3618 (-OH), 3450 (-NH), 1656 (-NH-**C=O**), 1054 (-CH_2-**OH**) cm^{-1}.

6h: $C_{13}H_{11}NO_2$: calculated C 73.22, H 5.20, N 6.57; found C 73.13, H 5.31, N 6.68; mp 168-170 °C [lit.,[27] mp 170-171 °C]; ^{1}H-NMR (DMSO-d_6) δ 4.42 (s, 1H), 6.32-6.40 (m, 4H, *J* = 1.9 Hz), 6.47-6.63 (m, 5H, *J* = 6.7 Hz), 8.85 (s, 1H).

6i: $C_{15}H_{15}NO$: calculated C 79.97, H 6.71, N 6.22; found C 79.86, H 6.68, N 6.36; mp 138-139 °C [lit.,[28] mp 138-139 °C]; ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H), 4.59-4.62 (d, 2H, *J* = 5.7 Hz), 6.48 (s, 1H), 7.18-7.21 (d, 2H, *J* = 7.9 Hz), 7.65-7.69 (d, 2H, *J* = 8.8 Hz).

6l: $C_{11}H_{13}NO_2$: calculated C 69.09, H 6.85, N 7.32; found C 69.21, H 6.79, N 7.41; mp 74 °C [lit.,[29] mp 73.8 °C]; ^{1}H-NMR ($CDCl_3$) δ 3.40-3.65 (m, 8H), 7.37-7.48 (m, 5H); IR ($CHCl_3$) ν 1624 (-N-**C=O**), 1433 (O=**C**-**N**-) cm^{-1}.

SSR (8): Prepared by reacting **3** with ethyl 2-methylacetoacetate as described for the preparation of **4**. IR (nujol) 1746 (-O-**C=O**), 1272 (-**O**-**C**=O), 1151 (-**C**-**O**-C=O) cm^{-1}.

ACKNOWLEDGMENTS

Functional support of this research by Istituto Superiore di Sanità, Roma, Italy (II Programma Nazionale di Ricerca sull'AIDS-1998, grant no. 40B.69 and III Programma Nazionale di Ricerca sull'AIDS-1999, grant no. 40C.65) as well as by University of Siena (PAR 1999) is gratefully acknowledged. M.B. wishes to thank the Merck Research Laboratories for the 2001 Academic Development Program (ADP) Chemistry Award.

REFERENCES AND NOTES

¶ Present address: GlaxoSmithKline Group, Glaxo Wellcome S.p.A, via Fleming 4, Verona (Italy).

1. R. J. Booth and J. C. Hodges, *Acc. Chem. Res.*, 1999, **32**, 16.

2. D. H. Drewry, D. M. Coe, and J. C. Poon, *Med. Res. Rev.*, 1999, **19**, 97.

3. P. Seneci, *La chimica e L'industria*, 2000, **82**, 386.

4. S. J. Shuttleworth, S. M. Allin, and P. K. Shamara, *Synthesis*, 1997, 1217.

5. S. Bhattachoryya, *Comb. Chem. & High Throughput Screening*, 2000, **3**, 65.

6. G. Cainelli, F. Manescalchi, and M. Panunzio, *Synthesis*, 1976, 472.

7. C. R. Harrison and P. Hodge, *Synthesis*, 1980, 299.

8. S. W. Kaldor, M. G. Siegel, J. E. Fritz, B. A. Dressman, and P. J. Hahan, *Tetrahedron Lett.*, 1996, **37**, 7193.

9. A. Mc Killop and D. W. Young, *Synthesis*, 1979, 401.

10. S. J. Shuttleworth, S. M. Allin, and P. K. Sharma, *Synthesis*, 1997, 1217.

11. D. Obrect and J. M. Villalgordo, *Tetrahedron Organic Chemistry Series*, 1998, **17**, 45.

12. D. Seebach, R. E. Marti, and T. Hintermann, *Helv. Chim. Acta*, 1996, **79**, 1710.

13. R. Ferritto and P. Seneci, *Drugs Futures*, 1998, **23**, 643.

14. S. Cheng, C. M. Tarby, D. D. Comer, J. P. Williams, L. H. Caporale, P. L. Myers, and D. L. Boger, *Bioorg. & Med. Chem.*, 1996, **4**, 727.

15. B. J. Cohen, M. A. Kraus, and A. Patchornik, *J. Am. Chem. Soc.*, 1981, **103**, 7620.

16. B. J. Cohen, M. A. Kraus, and A. Patchornik, *J. Am. Chem. Soc.*, 1977, **99**, 4165.

17. S. W. Kaldor, J. E. Fritz, J. Tang, and J. Mc Kinney, *Bioorg. & Med. Chem.*, 1995, **6**, 3041.

18. M. Botta, F. De Angelis, and R. Nicoletti, *Tetrahedron Lett.*, 1988, **29**, 2741.

19. F. Guillier, D. Orain, and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091. A. S. Hernandez and J. C. Hodges, *J. Org. Chem.*, 1997, **62**, 3153. F. Tiezte and A. Steinmetz, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 651. K. Ngu and D. V. Patol, *Tetrahedron Lett.*, 1997, **38**, 973. D. Obrecht, C. Abrecht, A. Grieder, and J. M. Villalgordo, *Helv. Chim. Acta*, 1997, **80**, 65.

20. X. Zhao, K. W. Jung, and K. D. Janda, *Tetrahedron Lett.*, 1997, **38**, 977.

21. A. H. Schulthess and H. J. Hansen, *Helv. Chim. Acta*, 1981, **64**, 1322.

22. G. P. Chiusoli, M. Costa, P. Pergreffi, S. Reverberi, and G. Salerno, *Gazz. Chim. Ital.*, 1985, **115**, 691.

23. H. H. Wasserman and P. S. Wharton, *J. Am. Chem. Soc.*, 1960, **82**, 661.

24. K. Sato, *Nippon Kagaku Zasshi*, 1955, **76**, 1404.

25. F. Messina, M. Botta, F. Corelli, M. P. Schneider, and F. Fazio, *J. Org. Chem.*, 1999, **64**, 3767.

26. V. Braun and A. Pinkernelle, *Chem. Ber.*, 1934, **67**, 1056.

27. A. L. LeRosen and E. D. Smith, *J.Am. Chem. Soc.*, 1948, **70**, 2705.

28. J. B. Hendrickson and Md. S. Hussoin, *J. Org. Chem.*, 1989, **54**, 1144.

29. M. L. Bender and J. M. Jones, *J. Org. Chem.*, 1962, **27**, 3771.