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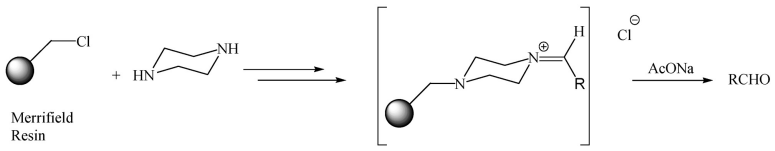

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The Use of Solid-Phase Supported 1-*N*-Piperazine-4-*N*-carboxaldehyde in Vilsmeier Reactions

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A Vilsmeier salt supported on solid phase was prepared using piperazine bound to Merrifield resin. Piperazine was selected because it contains two secondary amines: one of the amines is protected upon binding to the resin, and the second was formylated to give resin-1-*N*-piperazine-4-*N*-carboxaldehyde (**9**). Activation of the formamide with either bis(trichloromethyl)carbonate (BTC) or $POCl_3$ afforded the Vilsmeier salt **10**. Several olefins were used to test the supported Vilsmeier reagent. The in-solution activation with BTC and $POCl_3$ of various secondary amides was also evaluated: dimethylformamide (**1**), *N*-methyformanilide (**4**), 4-formylmorpholine (**5**), and 1,4-dicarboxylpiperazine (**6**), which showed that amides with one additional heteroatom increase the yields in the Vilsmeier salt formation.

Introduction

The growth of solid-phase organic synthesis (SPOS) has permitted the development of new techniques as well as their implementation. R. B. Merrifield originally developed this methodology on the basis of the use of a polystyrene resin as the solid support.[1] Supporting chemical reagents on a solid phase has been of great interest, since they show important advantages over those used in homogeneous systems. Reactions may be performed in a much cleaner manner, and greater product control may be achieved. A factor of importance in the design of the supported reagents is that the byproducts of decomposition remain bound to the polymeric support and can be reactivated for further use. It has been demonstrated that supported reagents are very useful for the efficient purification of combinatorial synthesis products.[2] Examples of these resins are PS-THP,[3] PS-isocyanate,[4] PS-carbodiimide,[5] PS-Ph_3P,[6] and PS-BOP,[7] among others.

The Vilsmeier process is frequently referred to as a formylation reaction in olefin systems.[8a,b] In general terms, the Vilsmeier reagent is formed when a secondary amide reacts with an acid halide as $POCl_3$, the most commonly used amide for this process being DMF.[9,10] The potential of carbon−carbon bond-forming reactions of chloromethyleneiminium salt involving aromatic and acyclic or alicyclic nuclei has been extensively studied.[11]

This reaction has been used in applications such as synthesis of an alkaloid hexahydropyrroloindolizine ring system,[12] systematic study of the reaction of alkyl-substituted 2-cyclohexen-1-ones with Vilsmeier reagents,[13] selective conversion of *O*-alkylsilyl ethers (*O*-TES, *O*-TBDMS, *O*-TBDPS, *O*-TIPS) to the *O*-formates,[14] ring closing of resin-bound diamines using Vilsmeier reagent to yield imidazolines,[15] facile N-formylation using formic acid and dicyclohexylcarbodiimide (DCC),[16] and synthesis of carbon-11-labeled *N*-formyl piperidine,[17] among others.

Results

Here, we report a simple method to generate a Vilsmeier-type salt supported on solid phase. The activation process of several secondary formamides was first tested in solution in order to select the best candidate for supporting on solid phase. In our laboratory, we have examined a variety of applications of bis(trichloromethyl)carbonate (BTC), also known as "triphosgene", as a substitute for either the $POCl_3$ or phosgene.[18] These applications include synthesis of quinazolinediones,[19] azaspiranes,[20] coupling of peptides (BOP and PyBOP),[21] conversion of alcohols to chlorides,[22] and so forth. Therefore, BTC was selected for the activation of DMF (**1**) to obtain the Vilsmeier reagent of chloromethyleneiminium salt (**2**). The mechanism for the formation of Vilsmeier reagent is shown in Scheme 1.

By monitoring ^1H NMR spectra at 25° C in $CDCl_3$, we have determined that the activation step requires ∼30 min for completion; the kinetics of activation was found to be first-order. The same reaction in CD_3CN occurs spontaneously. The NMR spectrum in $CDCl_3$ shows signals at δ_H 13.95 for the iminium hydrogen when an adduct is formed (**3**) and at δ_H 11.03 for the iminium hydrogen on the Vilsmeier reagent (**2**), according to the equilibrium shown in Scheme 2.

Other formamides (Figure 1) were also activated with BTC: *N*-methylformanilide (NMF) (**4**), 4-formylmorpholine (FMA) (**5**), and 1,4-dicarboxylpiperazine (DCP) (**6**).

The achieved activation yields for the formamides DMF (**1**), NMF (**4**), FMA (**5**), and DCP (**6**) was determined by NMR measurements and found to be 69, 41, 98, and 81%, respectively. A high activation was attained with the presence of a heteroatom on the amides **5** and **6**, possibly enhanced

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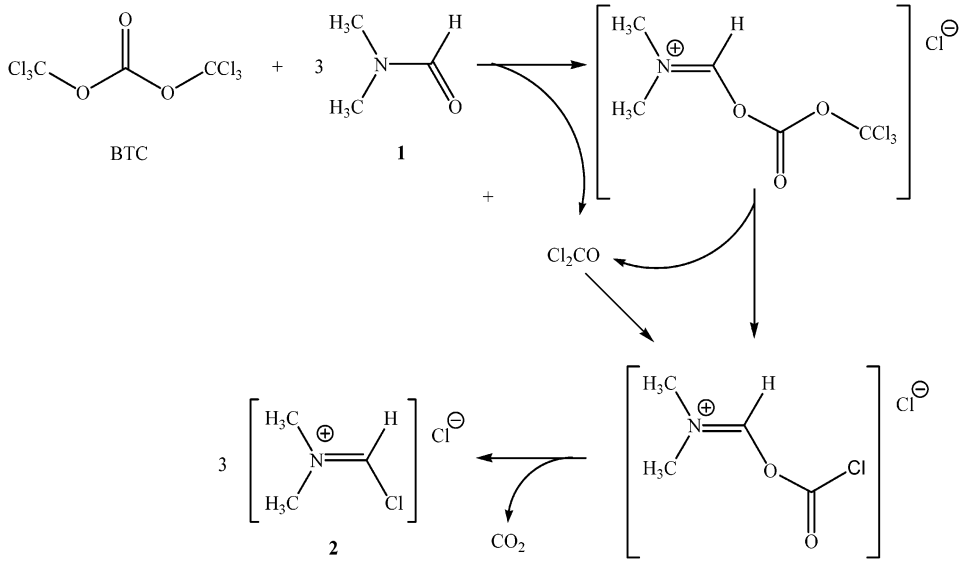
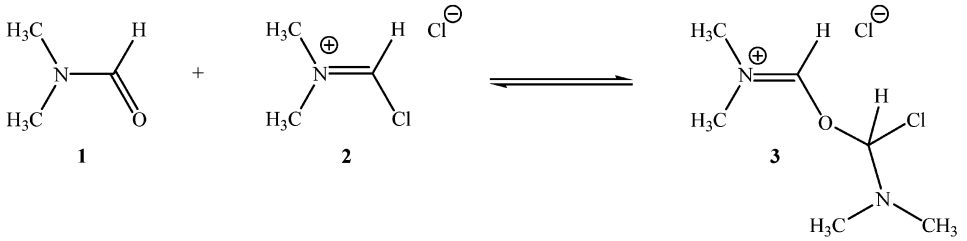
Scheme 1. Activation Mechanism of DMF with BTC



Scheme 2. Formation of the Less Active Adduct **3**



by its solubility and, therefore, obtaining a Vilsmeier salt with greater solubility.

Compounds **5** and **6** were the formamides with the highest activation degree, and the selection was made because **6**, having piperazine (**7**) as precursor, possesses excellent properties to be bound to the solid phase. One of the amino groups is attached to the resin, and the other could be formylated and activated to give the supported Vilsmeier salt.

Scheme 3 shows the methodology used to support piperazine (**7**) on Merrifield resin, obtaining resin-1-*N*-piperazine (**8**). The optimal conditions were established by means of chemistry in parallel for quantitative conversion. Formylation of resin **8** was carried out with different formylating agents, such as formic acid, triethylorthoformate, and ethyl formate. The latter was found to be the best reagent under mild conditions. In this way, resin-1-*N*-piperazine-4-carboxaldehyde (**9**) was obtained and then activated with either BTC or $POCl_3$ to give resin-1-*N*-piperazinylchloromethyliminium chloride (**10**). This resin was swollen in DCM, and various substrates were added to test the supported Vilsmeier salt:

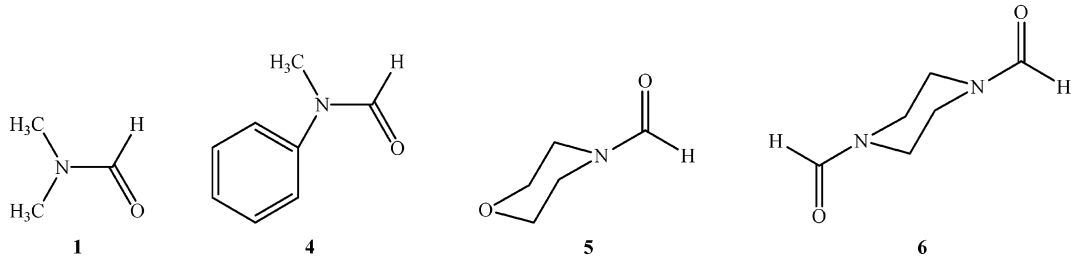
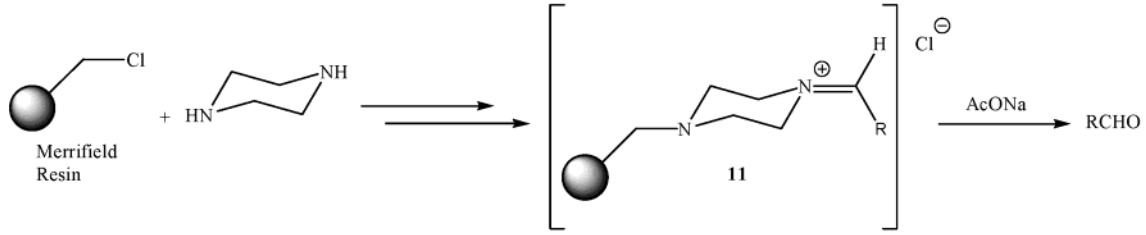


Figure 1. Secondary amides actived with BTC (triphosgene).

Scheme 3. Synthetic Route for the Synthesis of a Vilsmeier Salt Supported on Solid Phase (**10**) and Formation of a Formylated Product



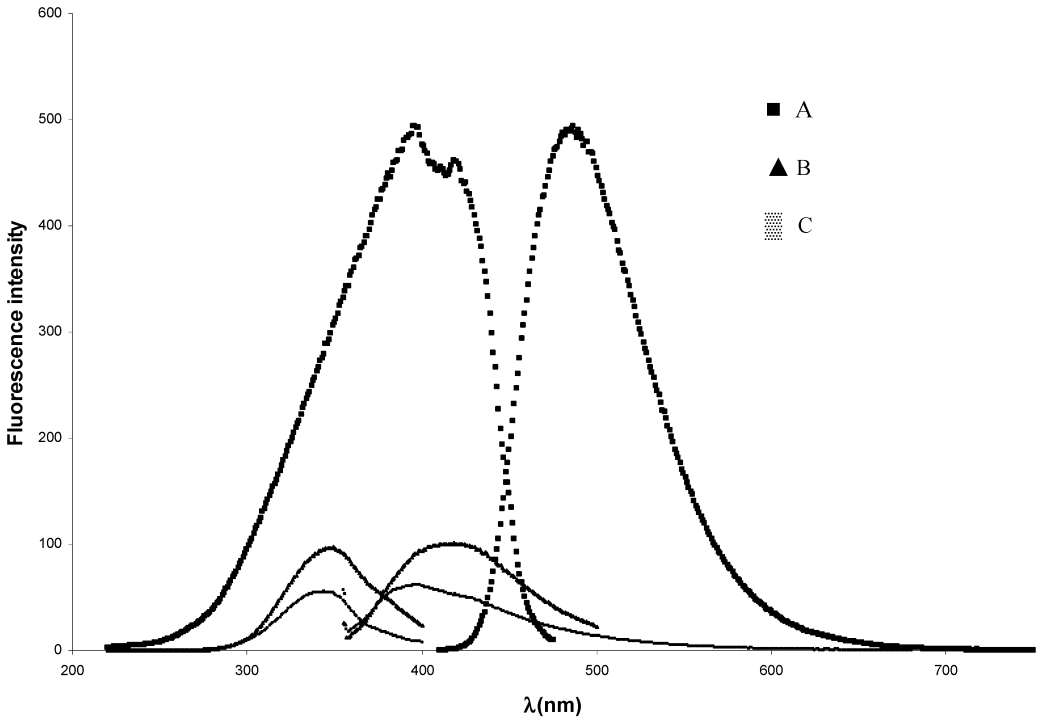
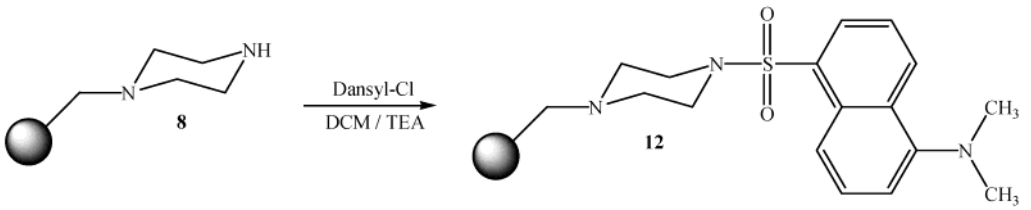


Figure 2. Fluorescence spectra of the dansylation test: (A) resin-1-*N*-piperazyl-4-*N*-dansyl (**12**). Em_{max}: 486 nm (Exc: 396 nm). (B) resin-1-*N*-piperazine (**8**). Em_{max}: 419 nm (Exc: 349 nm). (C) Merrifield resin, Em_{max}: 396 nm (Exc: 344 nm).

Scheme 4. Dansylation Test for Reaction Monitoring



1,3-dimethoxybenzene, 1,3-dihydroxybenzene,[23] *N*-methylpyrrole,[24−26] pyrrole, and 4-methylacetophenone. The supported salt **10** reacts with 1 equiv of the substrate to form an imidonio salt (**11**). In each case, the excess of substrate was removed by simple filtration, and then the resin was hydrolyzed to obtain the corresponding aldehydes and the resin-1-*N*-piperazine (**8**) (Scheme 3). This resin was recovered and could be activated for further use. The ongoing reaction is unimolecular, which prevents secondary reactions involving more than one formulation, due to the relatively large intermolecular distances within the resin (>100 Å).

Formilation of resin-1-*N*-piperazine (**8**) was established by a dansylation reaction (Scheme 4), which allows the evaluation of the conversion degree. Dansylation is a method with a high correlation index, giving accurate information of the conversion on each step. The secondary nitrogen of the supported piperazine remains free to react with dansyl chloride, yielding a sulfonamide (resin-1-*N*-piperazyl-4-*N*-dansyl) (**12**). The fluorescence signal increases as the supported sulfonamide concentration increases. The resin was compacted in a flow cell and measured directly on the solid state.

Fluorescence results of the dansylation step on resin-1-*N*-piperazine (**8**) are shown in Figure 2. The excitation and emission wavelengths of the dansyl group are similar in both solution and solid state; furthermore, these bands appear at longer wavelengths than those of the Merrifield resin. Therefore, the analytical evaluation in the emission region of **12** leads to considerably accurate measurements. These measurements were performed directly on the resin to obtain good reproducibility. This method for quantification of resin dansilation also showed a very good linearity ($r^2 = 0.991$) (Figure 3).

Conclusion

Our method for preparation of a supported Vilsmeier salt using BTC instead of $POCl_3$ requires mild reaction conditions, and the supported piperazinylchloromethyliminium chloride (**10**) acts as a mild formylating reagent. In the case of supported secondary amides, formation of the adduct **3**[27] (Scheme 2), is not possible, since the interaction of two amide molecules is not feasible. The amount of reagent can be controlled, and the ongoing reactions are unimolecular, preventing the reagent from reacting with more than 1 equiv of Vilsmeier salt.

This resin acts as a support of the type "catch and release", since it attaches chemically to the reagent, and upon hydrolysis of the complex, the formylated product is released, allowing the resin to be reactivated and used again. The dansylation reaction can be used as a sensor, allowing the evaluation of the progress of the formylation reaction with excellent reproducibility and linearity based on a fluorescence

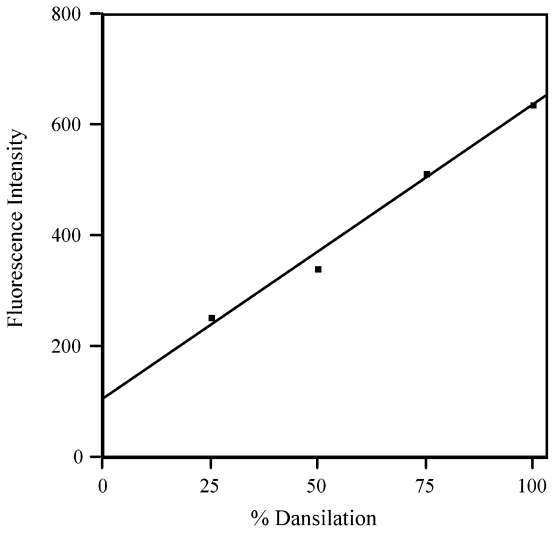


Figure 3. Calibration curve of the dansylation test of **8**.

technique. Measurements were performed directly on the solid material, showing its transparency for optical measurements, which allowed the evaluation of the supported substrate by means of the fluorescent sensor response.

Experimental Section

Melting points were measured on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 spectrometer in $CDCl_3$ with TMS as internal standard, at 200 and 50.289 MHz, respectively. Mass spectra were obtained on a Hewlett-Packard 5989 MS spectrometer at 70 eV by direct insertion. The purity was obtained on a high-pressure liquid chromatograph 1090 series II, column HP C-18. Fluorescence measurements were performed in a fluorescence spectrophotometer, Shimadzu RF-5301 PC. Combinatorial chemistry was carried out in a Reactor Quest Argonaut, model SLN-210.

Resin-1-*N*-piperazine (8). Merrifield resin (1.02 g, 1.08 mequiv of Cl) was placed in a 50-mL round-bottom flask and swollen with 15 mL of DMF for 15 min. Piperazine (**7**) (0.20 g, 2.32 mmol) and K_2CO_3 (1.61 g, 11.60 mmol) were added. The mixture was stirred for 6 h at 65 °C under inert atmosphere. The suspension was filtered and washed with DMSO (3 × 30 mL), CH_3OH (3 × 30 mL), water (3 × 30 mL), CH_3OH (3 × 30 mL), and DCM (3 × 30 mL). The resin was dried under high vacuum at RT, and the polymer-supporting yield was calculated according to Volhard titration of residual chlorine content in the Merrifield resin. Yield 95%. IR(KBr): 3426, 3036, 2913, 1379, 1600, 1487, 1441, 1143 cm^{-1}. FI = 99. Em_{max}: 419 nm (Exc: 349 nm).

Resin-1-*N*-piperazyl-4-*N*-dansyl) (12). Resin-1-*N*-piperazine (**8**) (20 mg, 0.02 mmol) was swollen with DCM (3 mL). TEA (50 μL, 0.35 mmol) and dansyl (6.42 mg, 0.02 mmol) in DCM (1 mL) were added. The reaction mixture was stirred under inert atmosphere at room temperature for 30 min, then filtered and washed with DCM (3 × 30 mL) and CH_3OH (3 × 30 mL). The product was dried under high vacuum at RT. IR (KBr): 3033, 2945, 2909, 2842, 1600, 1342, 1138, cm^{-1}. FI = 507. Em_{max}: 486 nm (Exc: 396 nm).

Resin-1-*N*-piperazine-4-carboxaldehyde (9). In a flask equipped with a 125-mL addition funnel, resin-1-*N*-piperazine (**8**) (1.05 g. 1.08 mmol) and 20 mL of methylformate were allowed to react under inert atmosphere with stirring at room temperature for 24 h. The formylated resin was filtered and washed with a solution of 1:1 dioxane and Na_2CO_3 (5%) (3 × 30 mL), CH_3OH (3 × 30 mL), and DCM (30 × 30 mL). The product was dried under high vacuum at RT. Yield, 95% (1.08 g 1.08 mmol). IR(KBr): 3026, 2913, 1676, 1594, 1492, 1446, 1164 cm^{-1}.

Resin-1-*N*-piperazinylchloromethyliminium Chloride (10). In a round-bottom flask, resin-1-*N*-piperazine-4-carboxaldehyde (**9**) (0.81 g, 0.862 mmol), was swollen in acetonitrile for 30 min. The mixture was placed in an ice bath under inert atmosphere with a reflux system. A solution of BTC in acetonitrile was added dropwise (0.12 g, 0.40 mmol). The reaction mixture was allowed to react for 1 h at 50−60 °C. The resin was filtered and washed with CH_3CN (3 × 30 mL) and DCM (30 × 30 mL). This resin was used directly in the next step.

General Procedure for Reaction Formylation in Solid Phase. 2,4-Dimethoxybenzaldehyde. The resin-1-*N*-piperazinylchloromethyliminium chloride (**10**) (0.5 g, 0.58 mmol) was swollen in $CHCl_3$ (10 mL), and 1,3-dimethoxybenzene (0.12 g, 0.86 mmol) was added to the reaction and stirred for 1 h. The reaction mixture was allowed to react for 1 h at reflux. The resin was filtered and washed with DCM (3 × 30 mL), then it was placed in a flask containing a solution of 1:1 dioxane and 5% sodium acetate and refluxed for 1 h. The mixture was filtered and washed with DCM (30 mL). The organic phase was separated and dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The product was obtained as a white solid (93%). mp 69−71 °C, (lit.[28] mp 69−72 °C). IR(KBr): 3031, 2919, 1677, 1596, 1487, 1444, 1261, 1119, 1022 cm^{-1}. ^{1}H NMR: δ 10.28 (s, 1H, C*H*O), 7.77 (d, 1H, J = 8.5 Hz), 6.52 (dd, 1H, J = 8.5, 2.1 Hz,), 6.42 (d, 1H, J = 2.1 Hz). EIMS *m*/*z*: [M$^+$] 166 (100), 149 (56), 135 (37), 120 (37), 106 (38), 77 (42), 63 (61).

2,4-Dihydroxybenzaldehyde. White crystalline solid (93%). mp 135−136 °C, (lit.[28] mp 135−137 °C). IR(KBr): 3126, 1636, 1605, 1499, 1441, 1232 cm^{-1}. ^{1}H NMR: δ 11.40 (s, 1H, O*H*), 9.70 (s, 1H, C*H*O), 7.41 (d, 1H, J = 8.5 Hz), 6.47 (dd, 1H, J = 8.5, 2.3 Hz), 6.38 (d, 1H, J = 2.3 Hz), 5.7 (br.s, 1H, O*H*). EIMS *m*/*z*: [M$^+$] 138 (76), 137 (100), 81 (18).

***N*-Methylpyrraldehyde.** Brown liquid (67%). bp 91−94 °C/35 mm, (lit.[28] bp 87−90 °C/22 mm). IR(KBr): 3100, 2921, 1700, 1550, 1435 cm^{-1}. ^{1}H NMR: δ 9.61 (d, 1H, J = 0.90 Hz, C*H*O), 6.93 (m, 2H, α',β) 6.19 (dd, 1H, β', J = 2.7, 2.4 Hz), 3.95 (s, 3H, Me). EIMS *m*/*z*: [M$^+$] 109 (100), 80 (33).

Pyrrole-2-carboxaldehyde. Yellow solid (73%). mp 43−44 °C, (lit.[28] mp 43−46 °C). IR(KBr): 3345, 2879, 1642, 1407, 1350, 1085, 1039 cm^{-1}. ^{1}H NMR: δ 10.03 (sa, 1H, N*H*), 9.56 (d, 1H, J = 0.9 Hz, C*H*O), 6.93 (m, 2H, α',β),

6.19 (dd, 1H, β', $J = 2.7$, 2.4 Hz). EIMS *m*/*z*: [M^+] 95 (100), 66 (72), 39 (55).

3-Chloro-3-(4′-methylphenyl)-2-propenaldehyde. Yellow liquid (95%). IR(KBr): 3033, 2918, 2851, 1666, 1595, 1128, 814 cm^{-1}. ^1H NMR: δ 10.19 (d, 1H, $J = 6.8$ Hz, C*H*O), 7.63 (d, 2H, $J = 8.4$ Hz), 7.25 (d, 2H, $J = 8.0$ Hz), 6.64 (d, 1H, $J = 6.8$), 2.39 (s, 3H, CH_3). ^{13}C NMR: δ 192.3, 130.1, 127.5, 123.0, 21.2. EIMS *m*/*z*: [M^+] 181 (10), 165 (100), 115 (50).

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References and Notes

(1) Merrifield, R. B. *Angew. Chem*. **1985**, *97*, 801; *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 799. (b) Merrifield, R. B. *Adv. Enzymol*. **1969**, *32*, 221. (c) Merrifield, R. B. *J. Am. Chem. Soc*. **1963**, *85*, 2149. (d) Barany, G.; Merrifield, R. B. *The Peptides*; Gross, E., Meienhofer, J., Ed.; Academic Press: New York, 1979; Vols. 2, 3.
(2) Booth, J.; Hodges, J. *Acc. Chem. Res*. **1999**, *32*, 18.
(3) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett*. **1994**, *35*, 9333.
(4) Rebek, J.; Brown, D.; Zimmermann, S. *J. Am. Chem. Soc*. **1975**, *97*, 4407.
(5) Parlow, J. J.; Mischke, D. A.; Woodard, S. S. *J. Org. Chem*. **1997**, *62*, 5908.
(6) (a) Licea-Claverie, A.; Rivero, I. A.; Morales, M. S.; Moreno, M. G. *Polym. Bull*. **1997**, *39*, 551. (b) Leadbeater, N. E. *J. Org. Chem*. **2001**, *66*, 2168.
(7) Rivero, I. A.; Acevez, R. *Rev. Soc. Quim. Mex*. **2000**, *44*, 97.
(8) (a) Hazebrouck, G. *Ann. Pharm. Fr*. **1966**, 24, 793. (b) Maheas, M. R. *Bull Chim. Fr*. **1989**, 1962.
(9) Meth-Cohn, O.; Tarnowski, B. *Adv. Heterocycl. Chem*. **1982,** *31*, 414.
(10) Pizey, J. S. *Synth. Reagents* **1974**, *1*, 1−99.
(11) (a) Meth-Cohn, O.; Stanforth, S. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 777. (b) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659. (c) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *Tetrahedron Lett*. **1979**, 3111.
(12) Sayah, B.; Pelloux-León, N.; Milet, A.; Pardillos-Guindet, J.; Vallée, Y. *J. Org. Chem*. **2001**, *66*, 2522.
(13) Katritzky, A. R.; Marson, Ch. M.; Wang, Z. *J. Org. Chem*. **1987**, *52*, 2730.
(14) Lellouche, J. P.; Koeller, S. *J. Org. Chem*. **2001**, *66*, 693.
(15) Acharya, A. N.; Thai, C.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem*. **2002**, *4*, 496.
(16) Effenberger, F.; Muck, A. O.; Bessey, E. *Chem. Ber*. **1980**, *113*, 6.
(17) Killbourn, M. R.; Jerabek, P. A.; Welch, M. J. *J. Chem. Soc., Chem. Commun*. **1983**, 861.
(18) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 894.
(19) Cortez, R.; Rivero, I. A.; Somanathan, R.; Aguirre, G.; Rámirez, F. *Synth. Commun*. **1991**, *21*, 285.
(20) Somanathan, R.; Rivero, I. A.; Núñez, G. I.; Hellberg, L. H. *Synth. Commun*. **1994**, *24*, 1483.
(21) Rivero, I. A.; Somanathan, R.; Hellberg, L. H. *Synth. Commun*. **1995**, *25*, 2185.
(22) Rivero, I. A.; Somanathan, R.; Hellberg, L. H. *Synth. Commun*. **1993**, *23*, 711.
(23) Mendelson, W. M.; Hayden, S. *Synth. Commun*. **1996**, *26*, 603.
(24) Silverstein, R. M.; Ryskiewicz, E. E.; Chaikin, S. W. *J. Am. Chem. Soc*. **1954**, *76*, 4485.
(25) Silverstein, R. M.; Ryskiewicz, E. E.; Willard, C.; Koehler, R. C. *J. Org. Chem*. **1955**, *20*, 668.
(26) Smith, C. F. *J. Chem. Soc*. **1954**, 3842.
(27) (a) Martin, G. J.; Martin, M. *Bull. Soc. Chim. Fr*. **1963**, 1637. (b) Martin, G. J.; Poignant, S. *J. Chem. Soc., Perkin Trans*. **1974**, *2*, 642. **(**c) Fritz, H.; Oehl, R. *Liebigs Ann. Chem*. **1971**, *749*, 159.
(28) Aldrich Chemical Co., Milwaukee, WI, 53201.

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