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Microwave-mediated Derivatization of Poly(styrene-*co*-allyl alcohol), a Key Step for the Soluble Polymer-assisted Synthesis of Heterocycles

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Abstract: Poly(styrene-*co*-allyl alcohol) can be readily esterified under classical conditions or under microwave irradiation. Some of the so-obtained polymers are effective precursors for the preparation of various nitrogen and oxygen heterocycles. The recycling of the polymeric auxiliary and its use in combinatorial chemistry are discussed. © 1999 Elsevier Science Ltd. All rights reserved.

The preparation and screening of combinatorial libraries of small molecules are becoming indispensable for drug discovery in the pharmaceutical industry. Till now, most of those libraries have been built on a solid support, generally a functionalized polystyrene resin cross-linked with 1-2 % divinylbenzene. Solid-phase organic synthesis (SPOS) makes purification and automation especially easy. However, when compared to solution-phase methods, SPOS generally requires time-consuming reaction development periods. In addition, industrial scale-up of SPOS for the preparation of fine chemicals is limited by the need for excess reagents to drive reactions to completion and by other problems due to the nature of heterogeneous reaction conditions. [1]

By substituting insoluble resins with soluble supports, *e.g.* polyethylene glycol and its derivatives, the familiar experimental procedures of classical organic chemistry are reinstated whereas product purification is made easier through macromolecular properties. The methodology is termed liquid-phase synthesis [2] or, less ambiguously, soluble polymer-assisted synthesis. It avoids the drawbacks of SPOS while preserving its positive aspects. Nevertheless, soluble polymer-assisted synthesis has been largely underestimated by organic chemists.

In connection with our research program on the exploitation of new methodologies to synthesize heterocyclic systems, [3] we considered that poly(styrene-*co*-allyl alcohol) **1**, having a structure intermediate between polystyrene

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and polyethylene glycol, may show the properties we desired. Surprisingly, this polymer has been rarely[4] used as a reagent, as indicated by an on-line search in the Chemical Abstracts file of STN-easy®.

Most of the target heterocycles prepared in our laboratory required a β-carbonyl ester or an enamino ester as precursor. Recent work of Tietze [5] reveals that such reactants can be readily bound to hydroxymethylated polystyrene through a transesterification reaction. Although we obtained a similar result by treating **1** with *t*-butyl 3-oxobutanoate in refluxing toluene for four hours, a more convenient procedure involved subjecting a neat mixture of the reagents to microwave irradiation,[6] which gave **2** in multigram quantities within a few minutes. The procedure was readily applied to the following esters: ethyl 3-oxobutanoate (→ **2**), ethyl 3-aminobut-2-enoate (→ **3**), ethyl 3-phenyl-3-oxopropanoate (→ **4**), and diethyl malonate (→ **5**). Polymers **8**, **9**, **12**, and **13** (Figure 1) were obtained from **1** and Hantzsch dihydropyridinedicarboxylates (**6**, **7**) or Hantzsch pyridinedicarboxylates (**10**, **11**) by classical reactions[7] in solution. In all cases, derivatization of the polymers was confirmed by routine IR, ^{1}H NMR, and ^{13}C NMR spectra, this being one of the main advantages of the soluble polymer-assisted synthesis methodology.

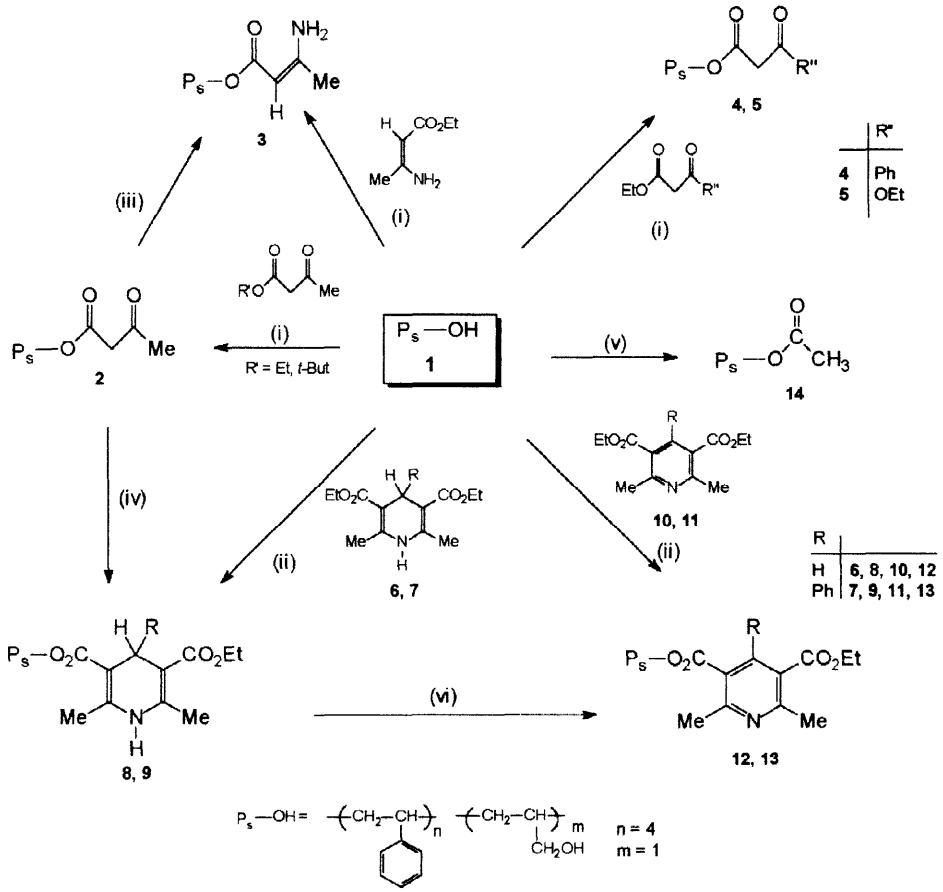

Fig. 1. Derivatization of **1**

The enamino carbonyl polymer **3** was also synthesized by reaction of **2** with ammonium acetate in refluxing benzene,[8] whereas the polymers bearing a dihydropyridine moiety, **8** and **9**, were obtained by a Hantzsch reaction from **2**, ethyl 3-oxobutanoate, an aldehyde, and ammoniac in hot ethanol. In addition, oxidation of **8** and **9** with cerium ammonium nitrate[9] in aqueous acetone at room temperature yielded samples exhibiting the same spectral characteristics as those recorded for the polymers (**12**, **13**) prepared by direct transesterification with the corresponding Hantzsch pyridinedicarboxylates.

In order to evaluate the synthetic potential of the polymeric esters we prepared, we studied their behaviour towards several electrophiles under well-known experimental conditions. In a first example (Figure 2), we considered the synthesis of the pyrazolo[3,4-b]pyridine-3,6-dione **16** by cyclocondensation of **2** with 5-amino-3,4-dihydro-2-phenyl-2*H*-pyrazole-3-one (**15**) in refluxing acetic acid.[10] The overall yield, based on the hydroxy content of **1** stated by the manufacturer, was 65 %, thus demonstrating the efficiency of both steps of the polymer-assisted preparation of **16**.

Recycling the polymeric auxiliary was achieved after isolation of the heterocycle **16** by filtration. Addition of water to the filtrate gave a precipitate that was identified as acetylated poly(styrene-*co*-allyl alcohol) **14**, on the basis of spectral analysis and comparison with **14** obtained unequivocally by treatment of poly(styrene-*co*-allyl alcohol) with hot acetic acid (Figure 1). Saponification of **14** gave a 60 % recovery of **1**, calculated on the weight used in the initial transesterification step.

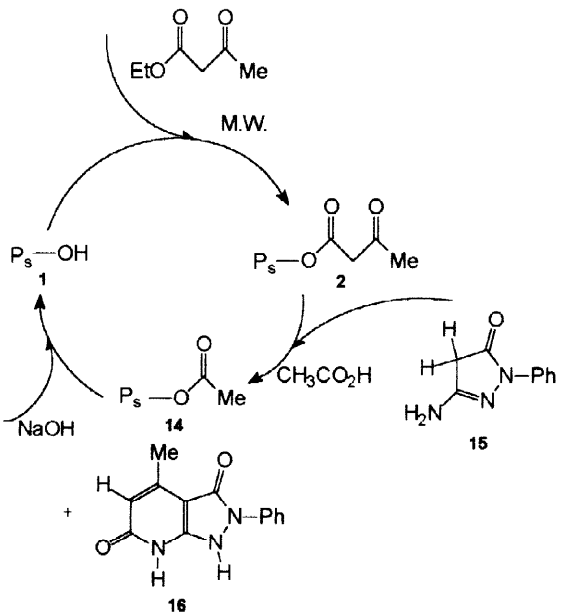

Fig. 2. Recycling process of **1**

As depicted in Figure 3, **15** reacts in a similar way with polymers **3** or **4**.

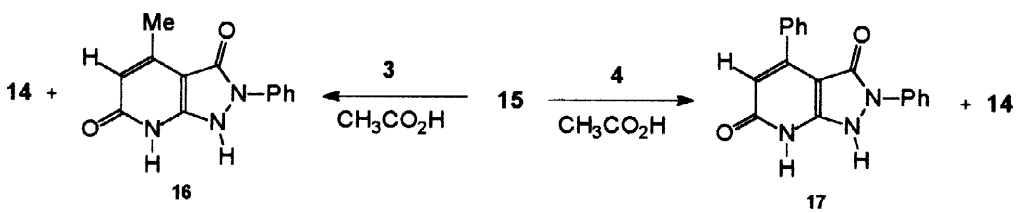

Fig. 3. Polymer-assisted synthesis of pyrazolo[3,4-b]pyridine-3,6-diones

We then tested the possibility of constructing fused oxygen heterocycles from 2-hydroxybenzaldehyde (**18**) and **2**, **4**, or **5**. We isolated the expected[11] coumarins **19**, **20**, or **21** (Figure 4) in 70, 30, and 45 % yield respectively (not optimized). It should be emphasized that **18** could react with **5** to yield two products : the free coumarin (**21**, ring closure with expulsion of the polymer) or poly(styrene-*co*-allyl alcohol) bearing the heterocycle (**22**, ring closure with expulsion of ethanol). In our hands, only the free coumarin only was isolated.

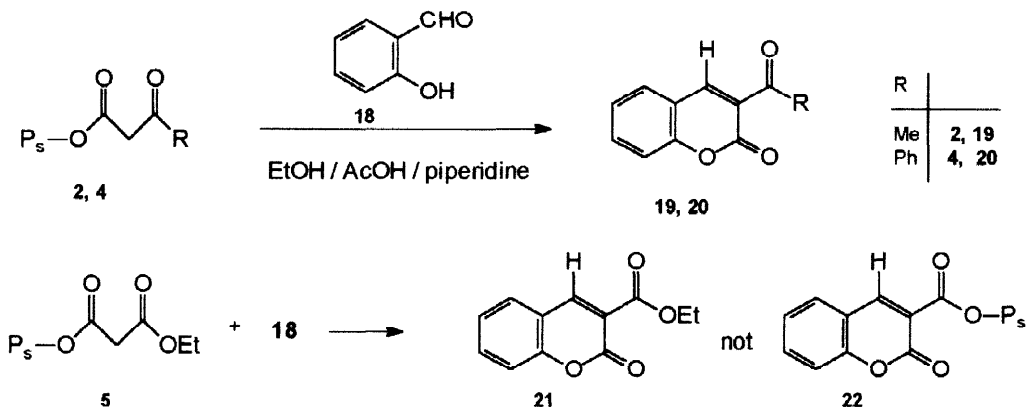

Fig. 4. Polymer-assisted synthesis of coumarins

The foregoing experiments demonstrate that poly(styrene-*co*-allyl alcohol) **1** can be readily functionalized, under microwave irradiation and solventless conditions, and that it constitutes an excellent auxiliary for the synthesis of various small molecules. The protocols disclosed herein make possible the preparation of heterocycles with several independently variable substituents, and therefore could be suitable for a combinatorial approach.[1a, 1c, 12] For example we observed, by ^{1}H NMR, that the reaction between 2-hydroxybenzaldehyde **18** and a mixture of the three polymers **2**, **4**, and **5** effectively yielded a mixture of the three expected coumarins **19**, **20**, and **21**. The application of this new method to a wider range of derivatives is now under way in our laboratory.

EXPERIMENTAL

Poly(styrene-*co*-allyl alcohol) was obtained from Aldrich Co. β-Keto esters, ethyl 3-aminobut-2-enoate, diethyl malonate, aldehydes (including **18**), cerium ammonium nitrate, ammonium acetate, ammoniac, benzene, toluene, acetic acid, ethanol, acetone, and compound **15** are commercially available (Aldrich Co, Acros Organics, Merck) and were used without further purification. IR spectra were recorded on a Perkin-Elmer FTIR 1760K spectrophotometer. NMR spectra were recorded on a Varian EM 360-L spectrometer (60 MHz for ^{1}H at 1.4 T) or a Bruker AMX spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C at 7.0 T). Chemical shifts are given in ppm using TMS as internal reference. Melting points (uncorrected) were determined on a hot-stage microscope. Solventless reactions were performed in a Whirpool AKL260 domestic microwave oven. Elemental analyses were carried out at the Station de Haute Belgique (Libramont-Chevigny, Belgium).

Compounds **6**,[7, 13] **7**,[7, 14] **10**,[7, 15] **11**,[7, 16] **16**,[10, 17] **17**,[10] **19**,[18] **20**,[19] and **21**[11, 20] have been described in the literature.

Preparation of 2. Procedure A: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and *tert*-butyl 3-oxobutanoate (0.79 g; 0.83 mL; 5 mmol) in toluene (50 mL) was heated under reflux for 4 hours. After cooling, **2** was precipitated with petroleum ether. The solvent was separated and the polymer was washed with boiling petroleum ether (to remove the unreacted ester and *tertio*-butanol). Procedure B: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and *tert*-butyl 3-oxobutanoate (0.79 g; 0.83 mL; 5 mmol) was irradiated in a domestic microwave oven for 5 minutes at a power of 400 W. The resulting product was washed with boiling petroleum ether. Procedure C: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and ethyl 3-oxobutanoate (0.65 g; 0.64 mL; 5 mmol) was irradiated in a domestic microwave oven for 10 minutes at a power of 400 W. The resulting product was washed with boiling petroleum ether. Procedure C has been scaled up to 10 g of **1** (irradiation time: 10 min). M.p.: 52-58 °C. IR (KBr): 700, 1151, 1239, 1316, 1454, 1494, 1718, 1742, 2923 cm^{-1}. ^1H NMR ($CDCl_3$): 2.2 (CH_3), 3.4 (CH_2CO) ppm. ^{13}C NMR ($CDCl_3$): 167.0, 200.6 ppm.

Preparation of 3. Procedure A: a mixture of poly(styrene-*co*-allyl alcohol) **1** (2 g) and ethyl 3-aminobut-2-enoate (1.29 g; 10 mmol) was irradiated in a domestic microwave oven for 10 minutes at a power of 400 W. The resulting product was washed with boiling petroleum ether. Procedure A has been scaled up to 10 g of **1** (irradiation time: 20 min). Procedure B: a mixture of **2** (1 g), ammonium acetate (0.8 g; 10 mmol), and acetic acid (0.5 mL) in benzene (25 mL) was heated under reflux and water was azeotropically distilled in a Dean-Stark apparatus. After cooling, the organic layer was washed with a saturated aqueous solution of sodium hydrogenocarbonate (2 X 25 mL), decanted, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting product was washed with boiling petroleum ether. M.p.: 70-78 °C. IR (KBr): 700, 1163, 1288, 1453, 1494, 1562, 1621, 1667, 2925, 3436 cm^{-1}. ^1H NMR ($CDCl_3$): 1.9 (CH_3), 5.5 (=CH) ppm. ^{13}C NMR ($CDCl_3$): 160.3, 171.0 ppm.

Preparation of 4. A mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and ethyl 3-phenyl-3-oxopropanoate (0.96 g; 0.87 mL; 5 mmol) was irradiated in a domestic microwave oven for 10 minutes at a power of 400 W. The resulting product was washed with boiling petroleum ether. The procedure has been scaled up to 10 g of **1** (irradiation time: 20 min). M.p.: 48-55 °C. IR (KBr): 700, 1193, 1266, 1452, 1687, 1740, 2924 cm^{-1}. ^1H NMR ($CDCl_3$) : 3.9 (CH_2CO), 7.6-8.0 (Ar) ppm. ^{13}C NMR ($CDCl_3$) :167.5, 192.2 ppm.

Preparation of 5. A mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and diethyl malonate (0.80 g; 0.76 mL; 5 mmol) was irradiated in a domestic microwave oven for 10 minutes at a power of 400 W. The resulting product was washed with boiling petroleum ether. The procedure has been scaled up to 10 g of **1** (irradiation time: 20 min). M.p.: 65-72°C. IR (KBr): 700, 1032, 1152, 1331, 1453, 1494, 1735, 1751, 2926 cm^{-1}. ^1H NMR ($CDCl_3$): 1.3 (CH_3), 3.3 (CH_2CO), 4.2 (OCH_2) ppm. ^{13}C NMR ($CDCl_3$): 166.4, 166.6 ppm.

Preparation of 8. Procedure A: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and diethyl 1,4-dihydro-2,6-dimethylpyridinedicarboxylate **6** (1.27 g; 5 mmol) in toluene (50 mL) was heated under reflux for 4 hours. After evaporation of the solvent under reduced pressure, the residue was washed with ethanol (to remove the unreacted materials). Procedure B: a mixture of polymer **2** (obtained by derivatization of 2 g of **1** under microwave irradiation), ethyl 3-oxobutanoate (0.52 g; 0.51 mL, 4 mmol), aqueous formaldehyde (33 %, 0.5 mL), and ammoniac (25 %, 0.7 mL) in ethanol (5 mL) was heated under reflux for 8 hours. The precipitate was filtered and washed with ethanol. M.p.: 85-90 °C. IR (KBr): 699, 1029, 12229, 1363, 1453, 1601, 1655, 1719, 2851, 2920, 3421 cm^{-1}. No NMR spectra could be recorded because of the poor solubility of the derivative.

Preparation of 9. Procedure A: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridinedicarboxylate **7** (1.65 g; 5 mmol) in toluene (50 mL) was heated under reflux for 4 hours. After evaporation of the solvent under reduced pressure, the residue was washed with acetonitrile (to remove the

unreacted materials). Procedure B: a mixture of polymer **2** (obtained by derivatization of 2 g of **1** under microwave irradiation), ethyl 3-oxobutanoate (0.52 g; 0.51 mL, 4 mmol), benzaldehyde (0.42 g; 0.41 mL; 4 mmol), and ammoniac (25 %, 0.7 mL) in ethanol (5 mL) was heated under reflux for 8 hours. The precipitate was filtered, and washed with acetonitrile. M.p.: 70-77 °C. IR (KBr): 700, 1151, 1210, 1248, 1309, 1453, 1494, 1718, 2922 cm^{-1}. ^1H NMR (DMSO d_6): 1.1 (CH_3 of the ester group), 2.5 (2,6-CH_3), 4.0 (OCH_2, q), 7.0-7.6 (Ar) ppm.

Preparation of 12. Procedure A: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and diethyl 2,6-dimethylpyridinedicarboxylate **10** (1.25 g; 5 mmol) in toluene (50 mL) was heated under reflux for 4 hours. After evaporation of the solvent under reduced pressure, the residue was washed with acetonitrile (to remove the unreacted materials). Procedure B: an aqueous solution of cerium ammonium nitrate (2.19 g; 4 mmol in 3.5 mL of water) was rapidly added dropwise into a suspension of polymer **8** (2 g) in acetone (15 mL). The mixture was heated under reflux until complete disappearance of the orange color (1 hour). After concentration under reduced pressure, the residue was treated with water (20 mL) and extracted with dichloromethane (2 X 30 mL). The organic layers were combined, washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, and the solvent was eliminated under reduced pressure. M.p.: 52-60 °C. IR (KBr): 1029, 1106, 1286, 1453, 1463, 1494, 1723, 2850, 2918, 3025 cm^{-1}. ^1H NMR ($CDCl_3$): 1.25 (CH_3 of the ester group, t), 2.9 (2,6-CH_3), 4.4 (OCH_2, q) ppm. ^{13}C NMR ($CDCl_3$): 162.5, 165.5 ppm.

Preparation of 13. Procedure A: a mixture of poly(styrene-*co*-allyl alcohol) **1** (1 g) and diethyl 2,6-dimethyl-4-phenylpyridinedicarboxylate **11** (1.63 g; 5 mmol) in toluene (50 mL) was heated under reflux for 4 hours. After evaporation of the solvent under reduced pressure, the residue was washed with acetonitrile (to remove the unreacted materials). Procedure B: an aqueous solution of cerium ammonium nitrate (2.19 g; 4 mmol in 3.5 mL of water) was rapidly added dropwise into a suspension of polymer **9** (2 g) in acetone (15 mL). The mixture was heated under reflux until complete disappearance of the orange color (1 hour). After concentration under reduced pressure, the residue was treated with water (20 mL) and extracted with dichloromethane (2 X 30 mL). The organic layers were combined, washed with an saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. M.p.: 80-85 °C. IR (KBr): 699, 758, 1029, 1452, 1494, 2850, 2921 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (CH_3 of the ester group, t),2.7 (2,6-CH_3), 4.3 (OCH_2, q), 7.0-7.5 (Ar) ppm. ^{13}C NMR ($CDCl_3$) : 166.4, 204.1 ppm.

Preparation of 16 and saponification of 14. Procedure A: a mixture of polymer **2** (obtained by derivatization of 2 g of **1** under microwave irradiation) and 5-amino-3,4-dihydro-2-phenyl-1*H*-pyrazole-3-one **15** (0.70 g; 4 mmol) in acetic acid (10 mL) was heated under reflux for 4 hours. After cooling, the precipitate was filtered and washed with water. Yield: 65 % based on the hydroxy content of 2 g of **1** , *i.e.* 5 meq. Addition of water to the first filtrate caused the precipitation of **14** in 60 % overall yield (weight). A mixture of **14** in an aqueous solution (5 mL, 5 M) of sodium hydroxide was heated under reflux for 4 hours. After cooling, the precipitate was filtered and washed with water to yield **1**. Procedure B: a mixture of polymer **3** (obtained by derivatization of 2 g of **1** under microwave irradiation) and 5-amino-3,4-dihydro-2-phenyl-1*H*-pyrazole-3-one **15** (0.70 g; 4 mmol) in acetic acid (10 mL) was heated under reflux for 4 hours. After cooling, the precipitate was filtered and washed with water. Yield: 65 % based on the hydroxy content of 2 g of **1** , *i.e.* 5 meq. M.p.: 297-300 °C. IR (KBr) : 755, 1301, 1355, 1378, 1432, 1457, 1499, 1595, 1636, 1662, 2850 cm^{-1}. ^1H NMR (DMSO d_6): 2.3 (CH_3), 6.0 (5-H), 7.2-7.8 (Ar) ppm. $C_{13}H_{11}N_3O_2$ (241.25): Calc. C, 64.72; H, 4.60; N, 17.42; Found C, 65.08; H 4.85; N, 17.00.

Preparation of 14. Poly(styrene-*co*-allyl alcohol) **1** (2 g) was heated in boiling acetic acid for 4 hours. After cooling, **14** was precipitated by addition of water. The solid was thoroughly washed with water. M.p.: 77-81 °C. IR (KBr): 701, 760, 1032, 1240, 1453, 1494, 1738, 2926, 3026 cm^{-1}. ^1H NMR ($CDCl_3$): 2.0 (CH_3) ppm. ^{13}C NMR ($CDCl_3$): 172.0 ppm.

Preparation of 17. A mixture of polymer **4** (obtained by derivatization of 2 g of **1** under microwave irradiation) and 5-amino-3,4-dihydro-2-phenyl-1*H*-pyrazole-3-one **15** (0.70 g; 4 mmol) in acetic acid (10 mL) was heated under reflux for 4 hours. After cooling, the precipitate was filtered and washed with water. Yield: 40 % based on the hydroxy content of 2 g of **1** , *i.e.* 5 meq. M.p.: 168-170 °C. IR (KBr): 754, 1381, 1430, 1457, 1471, 1597, 1607, 1631, 3432 cm^{-1}. ^1H NMR (DMSO d_6): 6.4 (5-H), 7.0-7.8 (Ar) ppm. $C_{18}H_{13}N_3O_2$ (303.32): Calc. C, 71.28; H, 4.32; N, 13.85; Found C,70.95; H, 4.01; N, 14.15.

Preparation of 19. A mixture of polymer **2** (obtained by derivatization of 10 g of **1** under microwave irradiation), 2-hydroxybenzaldehyde **18** (2.44 g; 2.14 mL; 20 mmol), piperidine (10 drops), and acetic acid (2 drops) in ethanol (10 mL) was heated under reflux for 4 hours. After cooling, the solution was concentrated under reduced pressure and the residue was treated with a mixture (1/1) of ethanol and water. Yield: 70 % based on the hydroxy content of 10 g of **1** , *i.e.* 25 meq. M.p.: 114-117 °C. IR (KBr) : 757, 980, 1211, 1367, 1455, 1558, 1614, 1679, 1741 cm^{-1}. ^1H NMR ($CDCl_3$): 2.8 (CH_3), 7.3-7.8 (Ar), 8.6 (4-H) ppm. $C_{11}H_8O_3$ (188.18): Calc. C, 70.21; H, 4.29; Found C, 69.85; H, 4.52.

Preparation of 20. A mixture of polymer **4** (obtained by derivatization of 10 g of **1** under microwave irradiation), 2-hydroxybenzaldehyde **18** (2.44g; 2.14 mL; 20 mmol), piperidine (10 drops), and acetic acid (2 drops) in ethanol (10 mL) was heated under reflux for 12 hours. After cooling, the solution was concentrated under reduced pressure and the residue was treated with a mixture (1/1) of ethanol and water. Yield: 30 % based on the hydroxy content of 10 g of **1** , *i.e.* 25 meq. M.p.: 118-120 °C. IR (KBr) : 682, 695, 939, 1245, 1454, 1568, 1610, 1657, 1714 cm^{-1}. ^1H NMR ($CDCl_3$): 7.3-8.1 (Ar), 8.2 (4-H) ppm. $C_{16}H_{10}O_3$ (250.25): Calc. C, 76.79; H, 4.03; Found C, 76.65; H, 3.75.

Preparation of 21. A mixture of polymer **5** (obtained by derivatization of 10 g of **1** under microwave irradiation), 2-hydroxybenzaldehyde **18** (2.44g; 2.14 mL; 20 mmol), piperidine (10 drops), and acetic acid (2 drops) in ethanol (10 mL) was heated under reflux for 4 hours. After cooling, the solution was concentrated under reduced presuure and the residue was treated with a mixture (1/1) of ethanol and water. Yield: 45 % based on the hydroxy content of 10 g of **1** , *i.e.* 25 meq. M.p.: 191-193 °C. IR (KBr): 1035, 1132, 1208, 1246, 1296, 1375, 1566, 1607, 1763 cm^{-1}. ^1H NMR ($CDCl_3$): 1.9 (CH_3, t), 4.5 (CH_2, q), 7.4-8.0 (Ar), 8.5 (4-H) ppm. $C_{12}H_{10}O_4$ (218.21): Calc. C, 66.05; H, 4.62; Found C, 66.38; H, 4.26.

Preparation of a mixture of 19, 20, and 21. A mixture of polymers **2** (obtained by derivatization of 1 g of **1** under microwave irradiation), **4** (obtained by derivatization of 1 g of **1** under microwave irradiation), **5** (obtained by derivatization of 1 g of **1** under microwave irradiation), 2-hydroxybenzaldehyde **18** (0.90 g; 0.78 mL; 7.5 mmol), piperidine (1 drop), and acetic acid (trace) in ethanol (3 mL) was heated under reflux for 8 hours. After cooling, the solution was concentrated under reduced pressure, the residue was treated with a mixture (1/1) of ethanol and water, and the resulting mixture was analyzed by ^1H NMR.

REFERENCES AND NOTES

1. (a) Terret, N.K.; Gardner, M.; Gordon, D.W.; Kobylecki, R.J.; Steele, J. *Tetrahedron*, **1995**, *51*, 8135-8173. (b) Früchtel, J.S.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17-42. (c) Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2288-2337. (d) James, I.W. *Molecular Diversity*, **1996**, *2*, 175-180. (e) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron*, **1996**, *52*, 4527-4554. (f) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron*, **1997**, *53*, 5643-5678

2. (a) Shemyakin, M.M.; Ovchinnikov, Y.A.; Kinyushkin, A.A.; Kozhevnikova, I.V. *Tetrahedron Lett.*, **1965**, *27*, 2323-2327. (b) Mutter, M.; Hagenmaier, H.; Bayer, E. *Angew. Chem. Int. Ed. Engl.*, **1971**, *10*, 811-812. (c) Bayer, E.; Mutter, M., *Nature*, **1972**, *237*, 512-513. (d)Douglas, S.P.; Whithfield, D.M.; Krepinsky, J.J. *J. Am. Chem. Soc.*, **1991**, *113*, 5095-5097. (e) Ranucci, E.; Spagnoli, G.; Sartore, L.; Ferruti, P. *Macromol. Chem. Phys.*, **1994**, *195*, 3469-3479. (f) Bonara, G.M. *Applied Biochem. Biotech.*, **1995**, *54*, 3-17. (g) Douglas, S.P.; Whitfield, D.M.; Krepinsky, J.J. *J. Am. Chem. Soc.*, **1995**, *117*, 2116-2117. (h) Bonara, G.M.; Baldan, A.; Schiavon, O.; Ferruti, P.; Veronese, F.M. *Tetrahedron Lett.*, **1996**, *37*, 4761-4764. (i) Gravert, D.J.; Janda, K.D. *Chem. Rev.*, **1997**, *97*, 489-509. (j) Wentworth Jr., P.; Vandersteen, A.M.; Janda, K.D. *Chem. Commun.*, **1997**, 759-760.
3. (a) Maquestiau, A.; Mayence, A.; Vanden Eynde, J.J. *Tetrahedron Lett.* **1991**, *32*, 3839-3840. (b) Vanden Eynde, J.J.; D'Orazio, P.; Mayence, A.; Maquestiau, A. *Tetrahedron*, **1992**, *48*, 1263-1268. (c) Vanden Eynde, J.J.; Mayence, A.; Lor, P.; Van Haverbeke, Y. *Bull. Soc. Chim. Belg.*, **1995**, *104*, 387-392. (d) Vanden Eynde, J.J.; Fromont, D. *Bull. Soc. Chim. Belg.*, **1997**, *106*, 393-397.
4. Combining "RN = 25119-62-4" and "reactant" gave 17 answers, the most relevant is a European patent, Public. N° 0 449 488 A1, Applic. N° 91302394.1, **1991**, Inv. Moren D.M.; Heilman, S.M.; Krepski, L.R.; Rasmussen, J.K.
5. Tietze, L.F.; Steinmetz, A. *Synlett*, **1996**, 667-668.
6. (a) Abramovitch, R.A. *Org. Prep. Proced. Int.*, **1991**, *23*, 683-711. (b) Berlan, J. *Radiat. Phys. Chem.*, **1995**, *45*, 581-589. (c) Caddick, S. *Tetrahedron*, **1995**, *51*, 10403-10432. (d) Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.*, **1995**, *48*, 1665-1692. (e) Galema, S.A. *Chem. Soc. Rev.*, **1997**, *26*, 233-238. (f) Shui-Tein, C.; Ping-Hui, T.; Hui-Ming, Y.; Chi-Yue, W.; Kwo-Feng, H.; Shih-Hsiung, W.; Kung-Tsung, W. *J. Chin. Chem. Soc.*, **1997**, *44*, 169-182.
7. Norcross, B.E.; Clement, G.; Weinstein, M., *J. Chem. Educt.*, **1969**, *46*, 694-695.
8. Baraldi, P.G.; Simoni, D.; Manfredini, S. *Synthesis*, **1983**, 902-903.
9. Pfister, J.R. *Synthesis*, **1990**, 689-690.
10. Van Haverbeke, Y.; Maquestiau, A.; Vanden Eynde, J.J., *J. Heterocycl. Chem.*, **1979**, *16*, 773-777.
11. Fitton, A.O.; Smally, R.K. *Practical Heterocyclic Chemistry*; Academic Press: London. 1968.
12. (a) Lowe, G. *Chem. Soc. Rev.*, **1995**, 309-317. (b) Gordon, E.M.; Gallop, M.A.; Patel, D.V. *Acc. Chem. Res.*, **1996**, *29*, 144-154. (c) Thompson, L.A.; Ellman, J.A. *Chem. Rev.*, **1996**, *96*, 555-600. (d) Frobel, K.; Krämer, T. *Chemie in unzere Zeit*, **1996**, *30*, 270-285. (e) Warr, W.A. *J. Chem. Inf. Comput. Sci.*, **1997**, *37*, 134-140. (f) Lam, K.S.; Lebl, M.; Krchnak, R.A. *Chem. Rev.*, **1997**, *97*, 411-448. (g) Nefzi, A.; Ostresh, J.M.; Houghten, R.A. *Chem. Rev.*, **1997**, *97*, 449-472. (h) Pirrung, M.C. *Chem. Rev.*, **1997**, *97*, 473-488.
13. Hantzsch, A. *Ann.*, **1882**, *215*, 1.
14. Schiff, R.; Puliti, J. *Chem. Ber.*, **1883**, *16*, 1607.
15. Engelman, F. *Justus Liebigs Ann. Chem.*, **1919**, *231*, 37.
16. Skraup, S. *Justus Liebigs Ann. Chem.*, **1919**, *419*, 58.
17. Taylor, E.C.; Barton, J.W. *J. Am. Chem. Soc.*, **1959**, *81*, 2448-2452.
18. Knoevenagel, E. *Chem. Ber.*, **1898**, *31*, 732.
19. Knoevenagel, E.; Arnot, A. *Chem. Ber.*, **1904**, *37*, 4497.
20. Knoevenagel, E. *Chem. Ber.*, **1898**, *31*, 2593.