Acknowledgment. Financial support from the CNR, Rome, Progetto Strategico "Processi di Trasferimento Monoelettronico", and Ministero della Pubblica Istruzione, Italy, is gratefully acknowledged.

Registry No. **1a**, 821-09-0; **1b**, 626-94-8; **1c**, 16744-89-1; **2a**, 65539-72-2; *cis*-**2b**, 113423-56-6; *trans*-**2b**, 113423-55-5; **2c**, 123883-67-0; **3a**, 1569-60-4; **3b**, 6090-15-9; *cis*-**4a**, 123883-68-1; *trans*-**4a**, 123883-69-2; **4b**, 114524-31-1; **5**, 625-31-0; **6**, 123883-70-5; **7**, 821-41-0; **8**, 75526-73-7; **9**, 1745-81-9; **10**, 66558-11-0; **11**, 123883-71-6; **12**, 123883-72-7; **13a**, 3508-78-9; **13b**, 59875-97-7; **13c**, 3897-04-9; **13d**, 123883-65-8; **14a**, 123883-73-8; **14b**, 123883-74-9; **14c**, 123883-75-0; **14d**, 123883-76-1; **15**, 30414-57-4; **16**, 76877-75-3; **17**, 109-49-9; *cis*-**18**, 123883-77-2; *trans*-**18**, 123883-78-3; **19**, 123883-79-4; **20**, 123883-80-7; **21**, 557-40-4; **22**, 75456-42-7; **23**, 123883-81-8; **24**, 591-80-0; **25**, 65234-93-7; **26**, 4219-24-3; **27**, 123883-82-9; **28**, 13668-61-6; **29**, 65234-92-6; **30**, 40637-56-7; *cis*-**31**, 123883-83-0; *trans*-**31**, 123883-84-1; **32**, 10283-95-1; **33**, 123883-85-2; **34**, 101347-54-0; **35**, 101347-60-8; **36**, 123883-66-9; **38**, 123883-86-3; $PhSe^{+}SO_4^{-}$, 123883-87-4; benzoylacetonitrile, 614-16-4; allyl bromide, 106-95-6; acetamide, 60-35-5; 2,2-dimethyl-4-pentenoyl chloride, 39482-46-7; diphenyl diselenide, 1666-13-3.

Reaction of 4-Substituted 2-Azetidinone with Nucleophiles. Existence and Reactivity of 1-Azetin-4-one

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Reaction of 4-acetoxy- or 4-sulfo-2-azetidinone with nucleophiles in the presence of a base has proven to be an elimination-addition process. Intermediate in this process is 1-azetin-4-one, whose free existence in solution, as well as its reactivity and stability, is shown in comparison with a five-member-ring counterpart. A new method for UV determinations of transient species is also described, showing its application to the elusive intermediate.

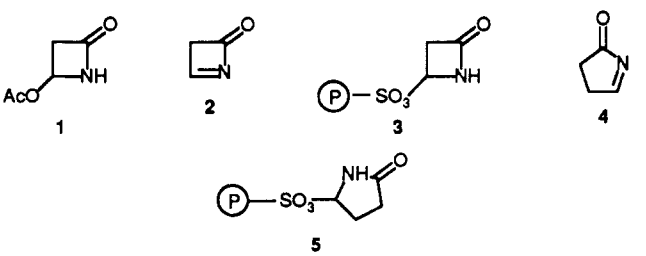
In our research about reactive heterocyclic intermediates[1] we were interested in studying the mechanism of substitution reaction of 4-acetoxy-2-azetidinone (**1**, Chart I) with nucleophiles. This is a very useful reaction in the preparation of a number of antibiotic compounds.[2] 1-Azetin-4-one (**2**) has been postulated by several authors as intermediate in the reactions of azetidin-2-ones in which substituents at position 4 are formally substituted by nucleophiles.[2a,3] In these reactions, the thermodynamic product is always formed, suggesting the reaction proceeds through a planar intermediate. Postulated azetinones of type **2** were also trapped by butadienes.[3b]

If intermediate **2** does exist, the reactions of β-lactams as **1** with nucleophiles will be not a substitution but an elimination-addition process. Thus, the first step in our work was to prepare an adequate precursor from which **2** could be easily obtained. This precursor, similar to **1**, was the polymer-bound 2-azetidinone, **3**.

Results and Discussion

Synthesis of Precursor 3. The synthesis of 4-polymeric sulfonate 2-azetidinone, **3**, was carried out by reaction between the sodium salt of polymeric sulfonic acid and 4-acetoxy-2-azetidinone (**1**). Polymeric sulfonic acid was prepared by hydrolysis of 20% cross-linked chlorosulfonated resin.[4] **3**: IR 1760, 1660, 1630, 1410, 1220-1180 cm^{-1}. Analysis indicated 0.16 mequiv azetidinone/g.

Chart I



The ability of **3** to act as a nonpolymeric analogue of **1**, was checked by reaction with sodium phenoxide. In the same conditions as the ones used by Clauss et al. for 4-acetoxy-2-azetidinone,[5] 4-phenoxy-2-azetidinone was obtained.

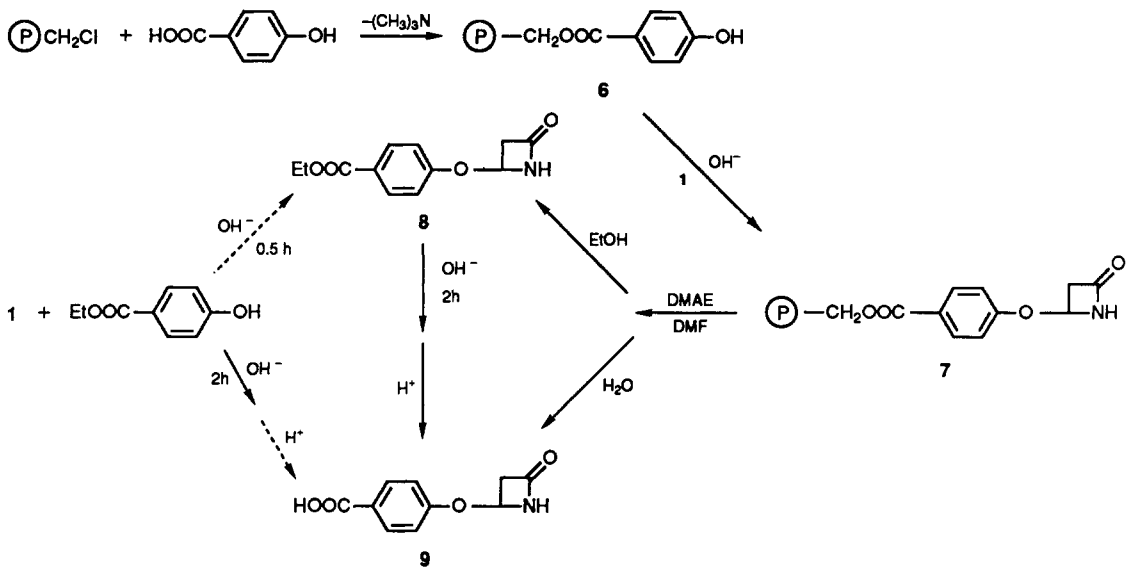
Three-Phase Test. The existence and reactivity of 1-azetin-4-one, **2**, was established by using the three-phase test.[4] As trapping agent, a nucleophilic polymer, **6**, was used; **6** was synthesized as shown in Scheme I. The Merrifield's resin reacted with *p*-hydroxybenzoic acid in the presence of triethylamine to give the polymeric ester **6** (IR 3000, 1700, 1600, 1450, 1370, 1260 cm^{-1}).

Polymer **6** was able to react with **1** in the presence of NaOH, as did their nonpolymeric counterparts, yielding **7** (Scheme I). Transesterification of **7** with dimethyl aminoethanol in DMF and then ethanol gave **8** (yield: 80%), identical with the compound obtained by reaction between **1** and *p*-hydroxybenzoic acid ethyl ester. This last reaction gave two different products depending on time. If the reaction time was short (less than 1 h) the product obtained was **8**. But if the reaction time was longer this product experienced a hydrolysis, yielding the acid **9**, after neutralization; **9** could also be obtained from **7** when ethanol was substituted by water during transesterification.

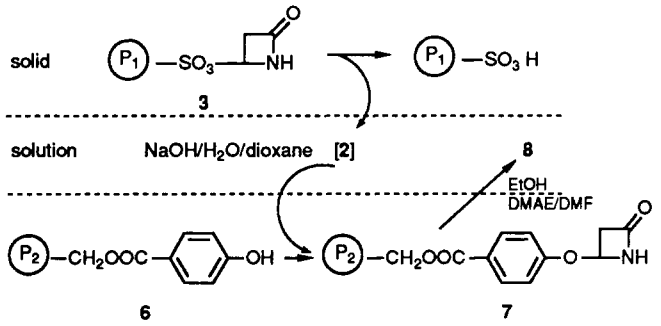
(1) Gaviña, F.; Costero, A. M.; Andreu, M. R.; Carda, M.; Luis, S. V. *J. Am. Chem. Soc.* **1988**, *110*, 4107-4108.
(2) (a) Kametani, T.; Honda, T.; Nakayama, A.; Sasakai, T.; Mochizuki, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228-2232. (b) Kraus, G. A.; Neuenschwanden, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134-135. (c) Kametani, T.; Chu, S. D.; Itok, A.; Maeda, S.; Honda, T. *J. Org. Chem.* **1988**, *53*, 2683-2687.
(3) (a) Attrill, R. P.; Barret, A. G. M.; Quayle, P.; van der Westhuize, J.; Bettes, M. J. *J. Org. Chem.* **1984**, *49*, 1679-1682. (b) Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1985**, *26*, 6309-6312. (c) Bachi, M. D.; Gross, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1157-1160.
(4) Rebek, J., Jr.; Gaviña, F. *J. Am. Chem. Soc.* **1975**, *97*, 1679-1682.
(5) Clauss, K.; Grim, D.; Prossel, G. *Justus Liebigs Ann. Chem.* **1974**, 539-560.

0022-3263/90/1955-0434$02.50/0

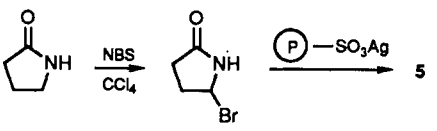
Scheme I



Scheme II



Scheme III



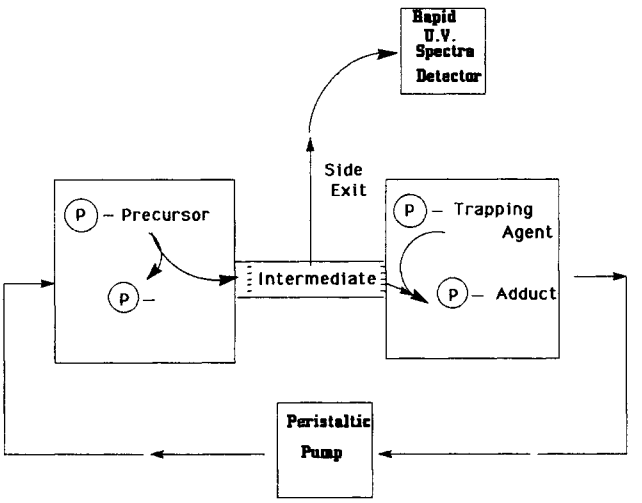


Figure 1. Scheme of three-phase experiments in PDRS.

For the three-phase experiment, polymers **3** and **6** were stirred in a solution of NaOH in water–dioxane, 1:1, at room temperature (Scheme II). Trapping polymer **6** was converted into polymeric azetidinone **7** as shown by yielding **8** (yield: 71%) after transesterification as indicated above. This experiment excluded any associative mechanism, as direct reaction between two different resin beads is not allowed. Appearance of **8** requires the generation of the intermediate **2** from precursor **3**.

Another pathway to products **7** and **8** could be a 3,4-elimination which generates an insaturated β-lactam isomeric with **2**. Apart from the fact that N-proton is the easiest proton to be transfered, Fedor[6] demonstrated that 3,3-dimethyl derivatives of 4-(aryloxy)azetidin-2-ones showed the same behavior with alkali as the 3-unsubstituted compounds. Thus 1,4-elimination must be the main process.

Behavior with Dienes. Comparison with 1-Azolin-5-one. Trapping of intermediate **2** as a dienophile was attempted by using some polymers functionalized with dienic groups, such as the 2-(polymeric carboxymethyl)-3-methyl-1,3-butadiene or the polymeric ester of 2-furoic acid, which have been good trapping agents for azacyclopentadienones.[1,7] Under the same experimental conditions for which the trapping of **2** by **6** was done, both dienic polymers were recovered unchanged.

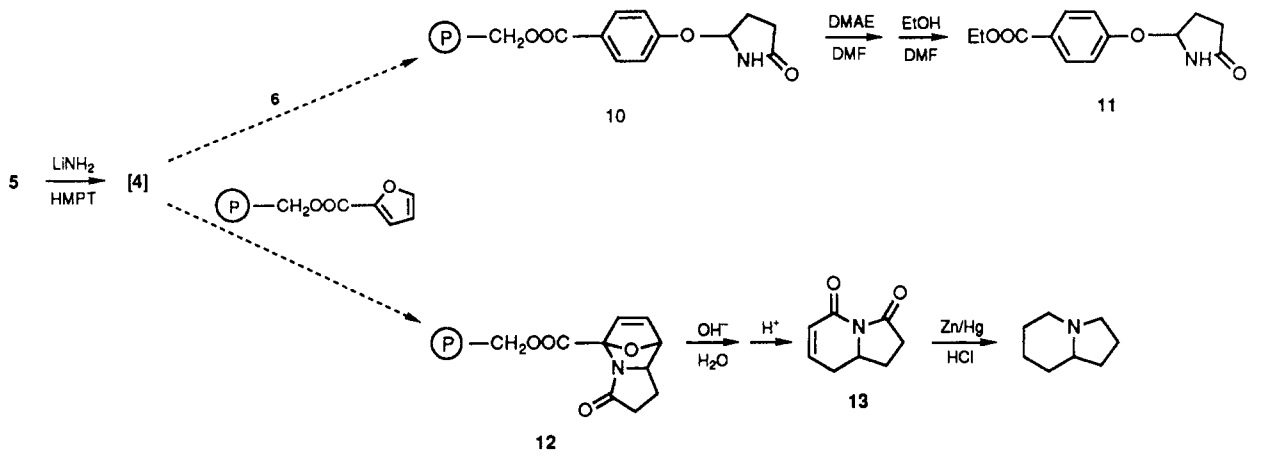
We thought of comparing **2** with its five-member-ring counterpart, 1-azolin-5-one, **4** (Chart I). As precursor for this species, polymeric sulfonate **5** was prepared as shown in Scheme III. 2-Pyrrolidone was brominated with NBS yielding 5-bromo-1-azolidin-2-one, which reacted with the silver salt of polymeric sulfonic acid[8] to give **5**.

Generation of **4** from **5** was demonstrated through three-phase experiments. For this, dienic as well as nucleophilic trapping agents were used (Scheme IV). When **5** was treated with $LiNH_2$ in the presence of **6**, polymer **10** resulted, from which ester–lactam **10** was isolated after transesterification. Reaction of **5** with polymeric furoate in DMSO yielded the polymeric adduct **12**, from which imidic compound **13** was obtained by basic hydrolysis followed by acidification. A Clemmensen reduction of **13**[1] gave δ-coniceine. Thus, **4** showed a dienophilic behavior, unlike the four-member-ring analogue **2**.

Lifetime Determinations. We have reported that the three-phase test can be adapted for lifetime determinations

(6) Fedor, L. R. *J. Org. Chem.* **1984**, *49*, 5094–5097.
(7) Gaviña, F.; Costero, A. M.; Andreu, M. R.; Luis, S. V. *J. Org. Chem.* **1988**, *53*, 6112–6113.
(8) Gaviña, F.; Costero, A. M.; Gil, P.; Palazón, B.; Luis, S. V. *J. Am. Chem. Soc.* **1981**, *103*, 1797–1798.

Scheme IV



of free intermediates in solution, through separation of the resins to a constant distance and introduction of a variable flow of the liquid phase, by using the so-called "polyphasic dynamic reactor" (PDR).[9]

We applied PDR to determine the lifetime for both intermediates, **2** and **4**, in the same conditions used with formerly studied heterocyclic intermediates. For that, polymeric precursors **3** and **5** and polymeric trapping agent **6** were used. A flow of basic solution was produced and adjusted by the use of a peristaltic pump (Figure 1). For 1-azetin-4-one (**2**), trapping by **6** was detected only for run times shorter than 2.0 ± 0.5 s, and the lifetime for this intermediate in these conditions must be stated in this value. The result obtained for 1-azolin-5-one (**4**) was 5.5 ± 0.5 s. Thus, 1-azetin-4-one is more unstable than 1-azolin-5-one. This higher unstability can be ascribed to the higher strain of the four-member ring, but also to the easy conversion of **2** into open 3-hydroxyacrylamide oxyanion.[6]

UV Determination. A conveniently modified PDR allowed us to apply, for the first time, a three-phase test experiment to obtain the UV spectrum of studied intermediate.

For that, PDR was provided with a side exit in the conduit which connected precursor and trap vessels. This side exit can be attached to a rapid spectra detector (for example a diode array UV detector) able to run a spectrum in a time shorter than intermediate lifetime.

We carried out the three-phase test with **3** and **6** in this modified PDR (we call it PDRS). When run time between precursor and trapping agent was shorter than 2 s, the side exit of PDRS was opened and the solution flowed through the UV rapid spectra detector (Figure 1). In this way we were able to have the UV spectrum. A wavelength of 246 nm fits quite well with the expected value for 1-azetin-4-one. For run times higher than 2.5 s the peak dissapeared, indicating that the spectrum corresponded to **2**, not to its decomposition products.

Conclusions

The free existence in solution of 1-azetin-4-one (**2**) and 1-azolin-5-one (**4**) has been demonstrated. The mechanism of the so-called nucleophilic substitution reactions of 4-substituted 2-azetidinone appears to follow in our experiences on polymers an elimination–addition pathway.

Reaction of **2** with dienes has not been detected. It could be due to its very short life (2 s) in our conditions. It looks as though Diels–Alder reactions with **2** were slower than its decomposition process. In the case of **4** its longer lifetime in our conditions allowed such a cycloaddition.

Polyphasic dynamic reactor has been applied, for the first time, to get the UV spectrum of a reactive intermediate.

Experimental Section

Polymeric Precursor 3. The sodium salt of polymeric sulfonic acid (9 g, 35.46 mequiv) was stirred with 12.51 g of 4-acetoxy-2-azetidinone (Aldrich) in 300 mL of CH_2Cl_2 at room temperature for 18 h. After the reaction mixture was filtered and washed with CH_2Cl_2, methanol, acetone, and ether, resin **3** was obtained: IR (KBr) 1760, 1660, 1630, 1410, 1220–1180, 1130, 1040, 1010, 830 cm^{-1}. Analysis (0.24% N) indicated 0.16 mequiv/g.

A 2.80-g (0.46-mequiv) sample of **3**, suspended in 100 mL of a solution of aqueous 2 N NaOH/dioxane, 1:1 (v/v), was stirred with 0.11 g (1.18 mequiv) of phenol at room temperature for 12 h. The solution was filtered, neutralized (1 N HCl), and then evaporated under vacuum, yielding a residuum. Extraction of this residuum with CH_2Cl_2 followed by chromatography (silica gel) of the solution gave 67 mg of 4-phenoxy-2-azetidinone, identical (melting point, IR, RMN) with an authentic sample.[5]

Trapping Polymer 6. Merrifield's chloromethylated resin (6 g, 7.44 mequiv) was suspended in 300 mL of dioxane containing 30 mL of triethylamine. Then 3.08 g of *p*-hydroxybenzoic acid was added, and the mixture was heated under reflux for 24 h. The resin was filtered and washed with dioxane, methanol, acetone, and ether to give **6**; IR (KBr) 3000, 1700, 1600, 1450, 1370, 1260, 1150, 1090, 1000 cm^{-1}. Saponification showed 2.30 mequiv ester/g.

A 1-g portion of **6** suspended in 100 mL of a solution of aqueous 2 N NaOH/dioxane, 1:1 (v/v), was stirred with 1.30 g of 4-acetoxy-2-azetidinone at room temperature for 10 h. After the reaction was complete, the filtered and washed resin, **7** (IR 3420, 3009, 2907, 1780, 1683, 1571, 1253, 1145 cm^{-1}; azetidinone content (by N analysis) 1.88 mequiv/g) was suspended in a mixture of 100 mL of DMF and 100 mL of DMAE and stirred at room temperature for 6 h.

The solution was filtered and distilled under vacuum, yielding an oil which was then dissolved in 50 mL of ethanol. The ethanolic solution was stirred at room temperature for 2 days and then distilled until 10 mL remained. Preparative TLC ($CHCl_3$) gave **8** (0.431 g, 80% yield): mp 184–186 °C; IR (KBr) 2059, 2915, 1800, 1675, 1589, 1369, 1296, 1239, 801 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 7.96 (d, 2 H), 7.90 (s, broad, 1 H), 7.04 (d, 2 H), 5.87 (t, 1 H), 4.29 (q, 2 H), 3.40 (dd, 1 H), 2.98 (dd, 1 H), 1.31 (t, 3 H); ^{13}C NMR ($(CD_3)_2CO$) δ 206.79 (COO), 166.25 (CONH), 160.95, 132.19, 124.75, 115.89, 76.74, 61.18, 46.45, 14.49; MS, m/z, 235, 234, 165, 137, 116, 76, 70. Anal. Calcd: C, 61.27; H, 5.53; N, 5.95. Found: C, 61.10; H, 5.35; N, 6.25.

Hydrolysis of **8** in aqueous 1 N NaOH/dioxane, 1:1 (v/v), under reflux for 2 h followed by neutralization yielded **9** as white crystals: mp 184–186 °C; IR (KBr) 3400–2500, 1758, 1650, 1430, 1150, 1110 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 7.93 (d, 2 H), 6.93 (d, 2 H), 5.6 (t, 1 H), 3.40 (dd, 1 H), 2.50 (dd, 1 H).

(9) Gaviña, F.; Costero, A. M.; Gil, P.; Luis, S. V. *J. Am. Chem. Soc.* **1984**, *106*, 2077–2080.

8 and 9 were also obtained through reaction of 1 (1.3 g) with *p*-hydroxybenzoic acid ethyl ester (1.6 g) suspended in 270 mL of aqueous 0.5 N NaOH. When the reaction mixture was heated under reflux for 0.5 h, 8 (35% yield) was obtained and identified. When the reaction time was longer than 2 h, only the acid 9 (52% yield) was obtained after acidification.

Three-Phase Experiment for 2. Precursor polymer 3 (17.5 g) and trapping polymer 6 (5.0 g) suspended in 1000 mL of a solution of aqueous 2 N NaOH/dioxane, 1:1 (v/v), were stirred at room temperature for 2 days. After this time, both solid phases were separated and washed with dioxane, acetone, and ether. Conversion of trapping phase into 7 was showed by IR. Azetidinone content in 7 (by N analysis): 0.45 mequiv/g. Transesterification of 7 as above indicated yielded 8 (0.465 g, 71% yield).

Synthesis of 5-Polymeric Sulfonate of 1-Azolidin-2-one (5). To 9.07 g of 2-pyrrolidone solved in 40 mL of CCl_4 was added 11 g of NBS in 40 mL of the same solvent, and the mixture was heated at 100 °C for 3 h. Then the reaction was chilled and filtered. The liquid was extracted twice with 30-mL portions of a cold aqueous solution of 25% $Na_2S_2O_3$, and then the organic phase was evaporated to dryness at reduced presure, giving 5-bromo-1-azolidin-2-one as a red-yellow oil: IR (KBr) 2950, 1750, 1660, 1420, 1290, 1180, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 7.9 (s broad, 1 H), 3.5 (t, 1 H), 2.3 (t, 2 H), 2.0 (m, 2 H).

The so-obtained 5-bromine-1-azolidin-2-one (5.25 g) was added to a suspension of 5 g of silver salt of polymeric sulfonic acid[8] in 500 mL of dioxane, under reflux for 3 days. Then the resin was filtered, washed with dioxane, and suspended in 700 mL of an aqueous solution of 5% KCN. The suspension was stirred at room temperature for 0.5 h and filtered. The resin was then washed with dioxane/water, 1:1, dioxane, acetone, and ether, yielding 5: IR (KBr) 3500–3300, 3060, 3020, 2910, 2900, 2840, 1600, 1490, 1430, 1250, 1030 cm^{-1}. Analysis (3.31% N) showed a functionalization of 2.36 mequiv/g.

Trapping of 4 by 6. 5 (1 g) and 6 (1 g) were suspended in 50 mL of HMPT. Lithium amide (4.5 g in 45 mL of HMPT) was added dropwise at 40 °C. After the reaction was stirred for an additional 16 h at room temperature, washing and then separation of the resins gave 10: IR 3390, 3000, 2900, 1660, 1560, 1480, 1440, 1360, 1250, 1140, 1000 cm^{-1}. Transesterification of 10 using the same conditions as for 7 gave 11 as a yellow oil: IR 2950, 1720, 1680, 1415, 1265, 1110, 1040, 810 cm^{-1}; ^1H NMR (CD_3OD) δ 7.75 (d, 2 H), 6.67 (d, 2 H), 5.65 (dd, 1 H), 4.16 (q, 2 H), 2.82 (m, 2 H), 2.40 (m, 2 H), 1.22 (t, 3 H); ^{13}C NMR (CD_3OD) δ 191.34 (COO), 181.16 (CONH), 166.40, 133.24, 119.68, 116.12, 97.18, 63.82, 40.99, 32.12, 14.98.

Three-Phase Reactions with a Dienic Trapping Agent. First, 1 g of 5 and 0.9 g of the polymeric ester of furoic acid[8] were suspended in 200 mL of HMPT–dioxane, 1:1. Then, 1 g of lithium amide in 100 mL of HMPT was added dropwise at 40 °C. The mixture was stirred at room temperature for 18 h. Resins were separated and washed with hot water, acetone, and ether. Furoate resin gave 12: IR 3550–3300, 2920, 2850, 1720, 1575, 1440, 1290, 1160, 1110, 990 cm^{-1}. Hydrolysis of 12 with 0.4 M KOH (dioxane–water, 1:1) under stirring and reflux for 2 days yielded the known hydroxybenzylic resin and a solution from which 13 could be isolated as an oil after acidification and preparative TLC (acetone–ethanol, 1:9): IR 3310, 2910, 2860, 1650, 1630, 1460, 1300, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56 (d, 1 H), 6.40 (m, 1 H), 3.35 (m, 1 H), 2.23 (t, 2 H), 2.0–2.10 (m, 4 H); MS *m/z* 151, 123, 83, 68, 55. Anal. Calcd: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.46; H, 6.10; N, 9.57. Reduction of 13 via the Clemmensen procedure[1] yielded the known compound octahydroindolizine (δ-coniceine), identical (IR, NMR, TLC) with an authentic sample.

Attempts to trap 2 by several polymeric dienes were carried out by the above indicated conditions. As an example, 2 g of precursor polymer 3 and 0.5 g of the polymeric ester of furoic acid were suspended in 40 mL of HMPT–dioxane, 1:1. Then, 1.5 g of lithium amide in 15 mL of HMPT was added dropwise at 45 °C. The mixture was stirred at room temperature for 24 h. Unchanged polymeric ester of furoic acid was then isolated.

PDR Lifetime Measurements. Lifetime measurements were taken as described.[9] In a series of experiments, a suspension of 0.5 mequiv of polymeric precursor, 3 or 5, with 0.5 g of lithium amide in HMPT was stirred at 35 °C in a vessel of PDR. Trapping agent 6 (0.9 mequiv) was stirred in the other vessel. Reagent solution flowed from precursor to trapping agent through a conduit of known volume. Lifetime experiments started as soon as the base was added. After each experiment, the polymeric trapping agent was tested for the presence of 7 or 10. This presence showed the transfer of intermediate 2 or 4, respectively, and a lifetime for this species higher than the run time. The lifetime values so obtained were 2.0 ± 0.5 s for 1-azetin-4-one (2) and 5.5 ± 0.5 s for 1-azolin-5-one (4).

Use of PDR for UV Determination (PDRS). The previously described PDR has been modified with a side exit in the conduit which connect precursor and trap vessels. This exit was provided with a tap and a glass–steel connection, which can be attached to a diode array rapid UV detector (LKB-2140). Three-phase experiments with 3 and 6 were carried out in PDRS as above indicated for lifetime determinations (Figure 1). When run time in central conduit was shorter than obtained lifetime for 2 (2 s), the tap was opened and the UV spectrum was detected as shown in Figure 1. At run times higher than 2.5 s this spectrum did not appear.

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Registry No. 1, 28562-53-0; 2, 104746-29-4; 4, 55047-80-8; 8, 123933-46-0; 9, 123933-47-1; 11, 123933-49-3; 13, 123933-52-8; phenol, 108-95-2; 4-phenoxy-2-azetidinone, 31898-84-7; *p*-hydroxybenzoic acid, 99-96-7; *p*-hydroxybenzoic acid ethyl ester, 120-47-8; 2-pyrrolidone, 616-45-5; 5-bromo-1-azolidin-2-one, 123933-48-2; octahydroindolizine, 13618-93-4.

Supplementary Material Available: Polyphasic dynamic reactor for spectra determinations (PDRS), UV spectrum of 1-azetin-4-one, and NMR spectra of 9 and 11 (5 pages). Ordering information is given on any current masthead page.