tration. The filtrate was washed with three 50-mL portions of water and dried over sodium sulfate. Four more batches similar to this were run, with a total of 2.1100 g (0.0160 mol) of bicyclic ketone **9**. These five batches were combined, and the ether was removed on the rotary evaporator to leave a yellow oil, which was distilled [45–47 °C (0.08 torr)] through a short-path column to yield 0.6237 g (4.720 mmol) of the title ketone **21** for a 30% yield. This ketone was slightly contaminated (about 10%) with another ketone identified as 1-indanone by comparison of its NMR spectrum with that of an authentic sample. The title ketone **21** has the following: NMR (100 MHz, $CDCl_3$) δ 6.53 (dd, J = 10, 5 Hz, 1 H, H-7), 6.00 (d, J = 10 Hz, 1 H, H-6), 5.84 (dddd, J = 5, 2, 1 Hz, 1 H, H-3), 5.54 (ddd, J = 5, 2, 1 Hz, 1 H, H-2), 3.38 (dd, J = 8, 2 Hz, 1 H, H-4), 2.90 (dt, J = 8, 2 Hz, 1 H, H-1), 2.61 (dq, J = 8, 1 Hz, 1 H, H-9), 2.03 (dt, J = 8, 5 Hz, 1 H, H-8).

Preparation of Tricyclo[6.1.0.0^{4,9}]nona-2,6-dien-5-one Tosylhydrazone (22). A 10-mL flask was charged with 0.399 g (3.02 mmol) of tricyclo[6.1.0.0^{4,9}]nona-2,6-dien-5-one (**21**) and 0.562 g (3.02 mmol) of tosylhydrazine dissolved in 6 mL of methanol. To this solution were added 2 drops of pyridine, and the solution was stirred at room temperature. The reaction was monitored by TLC (silica gel, chloroform). After 5 h, the starting ketone had reacted, and the reaction solution was placed in the freezer to induce crystallization. No crystallization had occurred after 24 h. The methanol was removed on the rotary evaporator and the resulting brown oil dissolved in warm ethanol. This was cooled in a freezer overnight to yield 0.0878 g (0.292 mmol, 10%) of tosylhydrazone: mp 141–143 °C dec; NMR (100 MHz, $CDCl_3$) δ 7.86 (d, J = 8 Hz, 2 H, aromatic protons), 7.60 (broadened s, 1 H, NH proton), 7.32 (d, J = 8 Hz, 2 H, aromatic protons), 6.38 (d, J = 9 Hz, 1 H, H-6 proton), 6.12 (m, 1 H, H-7), 5.77 (m, 1 H, vinyl proton), 5.47 (dd, J = 7, 2 Hz, 0.5 H, vinyl proton), 5.27 (dd, J = 7, 2 Hz, 0.5 H, vinyl proton), 4.20–3.50 (m, 1 H, H-4), 2.46 (s superimposed on m, 4 H, aromatic methyl and cyclopropyl protons), 2.22 (m, 1 H, cyclopropyl proton), 1.74 (m, 1 H, cyclopropyl proton); the product appears uncontaminated by 1-indanone tosylhydrazone as indicated by the absence of 1-indanone tosylhydrazone absorptions at δ 2.70 and 3.04; IR (Nujol mull), 3205 (m), 1642 (w), 1600 (m), 1350 (s), 1175 cm^{-1} (s); high-resolution mass spectrum, calcd for $C_{16}H_{16}N_2O_2S$ m/e 300.093, found m/e 300.093.

Decomposition of Tricyclo[6.1.0.0^{4,9}]nona-2,6-dien-5-one Tosylhydrazone (22) with Potassium Hydride and 18-Crown-6 in Diglyme. A 100-mL flask fitted with a magnetic stirrer and gas inlet was charged with 62.7 mg (0.345 mmol) of 22% potassium hydride in mineral oil. The potassium hydride was washed with five 5-mL portions of dry hexane. After removal of the last hexane wash, 10 mL of anhydrous diglyme was added and the flask thoroughly flushed with nitrogen. A solution of 75.6 mg (0.252 mmol) of the title tosylhydrazone **22** in 5 mL of diglyme was added to the stirred potassium hydride suspension. After the gas evolution had subsided, 67.3 mg (0.255 mmol) of 18-crown-6 in 3 mL of diglyme was added. The flask was fitted with a reflux condenser, and the reaction mixture was heated to 140 °C for 2.5 h. Upon cooling, it was poured into 200 mL of cold water and extracted three times with 60 mL of pentane. The pentane extracts were combined, washed five times with 100 mL of water, and dried over sodium sulfate. The pentane was removed by distillation through a 7-in. Vigreux column to leave about 0.5 mL of yellow oil which was analyzed by VPC (column C, 131 °C, 70 mL/min). Two compounds were present; the first at 12 min was identified as residual diglyme by VPC retention time and comparison of the NMR spectrum of the sample collected by preparative VPC with the spectrum of an authentic sample. The second compound at 18.5 min was identified as indene by VPC retention time and comparison of the NMR spectrum of the isolated compound (preparative VPC) with that of an authentic sample. No other compounds more than 3% of indene) were present by VPC. Tridecane internal standard was added, and the yield of indene was found to be 14%.

Decomposition of 1-Indanone Tosylhydrazone with Potassium Hydride in Tetrahydrofuran/Diglyme. A 100-mL flask fitted with a magnetic stirrer, reflux condenser, and gas inlet was charged with 97.5 mg (0.536 mmol) of 22% potassium hydride in mineral oil. The potassium hydride was washed five times with 10 mL of dry hexane, and after removal of the last hexane wash, 10 mL of anhydrous THF was added. To the stirred potassium hydride suspension was added 130.5 mg (0.435 mmol) of 1-indanone tosylhydrazone in 5 mL of THF. After the gas evolution had subsided, 111.6 mg (0.422 mmol) of 18-crown-6 in 5 mL of THF was added, and the reaction mixture was heated at reflux (65 °C) for 20 min. No nitrogen was evolved, so 22 mL of anhydrous diglyme was added, which raised the reflux temperature to 95 °C. The solution turned a deep blue-green color and was heated at reflux for 80 min. After cooling, the reaction mixture was poured into 150 mL of water, which resulted in the immediate loss of the blue-green color. This aqueous solution was extracted with four 40-mL portions of pentane. The combined pentane extracts were washed with five 100-mL portions of water and dried over sodium sulfate. The pentane was removed by distillation through a 7-in. Vigreux column to leave a small amount of yellow oil which was analyzed by VPC (column A, 125 °C, 65 mL/min). In addition to diglyme (9 min) two other products were found: an unidentified compound appeared at 11 min, and a compound identified as indene by comparison of its retention time at 14.8 min. The indene identification was verified by comparison of the NMR spectrum of the VPC-collected compound with that of an authentic sample. Dodecane internal standard was added, and the yield of indene was found to be 6.9% and that of the unknown 1.6%.

Registry No. 9, 17684-75-2; **10** (isomer 1), 81044-30-6; **10** (isomer 2), 81044-31-7; **10** Li salt (isomer 1), 81044-32-8; **10** Li salt (isomer 2), 81044-33-9; **11**, 95-13-6; **12**, 25928-15-8; **21**, 38898-62-3; **22**, 81044-34-0; 1-indanone tosylhydrazone, 73424-46-1.

Nucleophilic Displacement of Primary Amino Groups via 1-Substituted 4-Tosylimidazoles[1]

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Two methods are described for the replacement of primary amino groups, situated either α or γ to a heterocyclic nitrogen atom, by ethoxy, alkylthio, and arylthio substituents, by Wittig reagents, and by hydrogen. Both methods involve transformation of the primary amino group into a nucleofugic pendant heterocycle. The first converts the primary amino group into a 5-phenyl-1-tetrazolyl substituent by benzoylation, formation of the imidoyl chloride, and reaction with sodium azide, while the second converts the primary amino group into a 1-(4-tosylimidazolyl) substituent by reaction with triethyl orthoformate and acid to give the (ethoxymethylene)amino derivative, which is then condensed with tosylmethyl isocyanide (TosMIC) anion. The 1-(4-tosylimidazolyl) substituent is shown to be more susceptible to nucleophilic displacement by a wider range of nucleophiles.

Primary amino groups α to a heteroatom are among the most accessible of functional groups in heterocyclic systems because of their genesis either from terminal ring closure reactions involving intramolecular addition of an appro-

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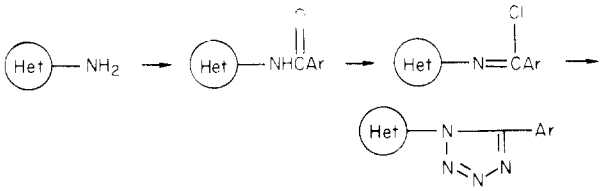
priate nitrogen, sulfur, or oxygen nucleophile to a nitrile or from the utilization of reagents such as guanidines, amidines, cyanamides, and thioureas in cyclization reactions. Despite their ubiquity, however, few useful synthetic methods are available for their conversion into other substituents.[3,4] We report in this paper on the development of a promising general method for the replacement of primary amino groups, situated either α or γ to a heterocyclic nitrogen atom, by ethoxy, alkylthio, arylthio, and certain carbon substituents as well as by hydrogen.

One possible approach to this problem involves conversion of the substituent amino group into a pendant heterocycle susceptible to nucleophilic displacement. For example, some amino-substituted heterocycles can be benzoylated without complication, and at least in one example, conversion to the corresponding imidoyl chloride followed by reaction with sodium azide has been reported to lead smoothly to tetrazole formation (e.g., 1).[5] We have



1, Het = 4-pyridyl; Ar = C_6H_5
2, Het = 4-pyridyl; Ar = $C_6H_4NO_2$-*p*
3, Het = 2-pyridyl; Ar = C_6H_5
4, Het = 1-isoquinolyl; Ar = C_6H_5

examined the synthesis and reactivity towards nucleophiles of several additional 5-aryl-1-tetrazolyl-substituted heterocycles.

Benzoylation of 2-aminopyridine was readily achieved with a slight excess of benzoyl chloride and pyridine as solvent at 100 °C for 1 h; 4-(*p*-nitrobenzamido)pyridine was similarly obtained in quantitative yield. More vigorous conditions were required, however, with less basic amines. For example, under the above conditions 1-aminoisoquinoline was only partially (25%) benzoylated; a 91% yield of 1-benzamidoisoquinoline was obtained only after 15 h. 4-Benzamidoquinazoline could not be obtained from 4-aminoquinazoline, benzoyl chloride, and triethylamine in either THF or toluene or by heating in neat benzoyl chloride; it was finally obtained in 87% yield by heating an equimolar mixture of 4-aminoquinazoline, benzoyl chloride, and triethylamine in xylene under reflux for 20 h. Similar drastic conditions were required for benzoylation of 2-amino-4-methylpyrimidine.

We experienced considerable difficulties in the conversion of some of the above benzamido derivatives to the requisite intermediate imidoyl chlorides. 4-Benzamidopyridine proved to be an optimal case; the imidoyl chloride was readily formed either by heating with PCl_5 at 140 °C for 45 min or by treatment with an excess of thionyl chloride at 60 °C for 4 h; without isolation, the crude imidoyl chloride was treated with aqueous sodium azide to give 1 in yields of 75% and 70%, respectively. Under the former conditions, 4-(*p*-nitrobenzamido)pyridine gave the tetrazole **2** in 80% yield, and 2-benzamidopyridine gave the tetrazole **3** in 50% yield. By contrast, however, 1-benzamidoisoquinoline decomposed rapidly in the presence of PCl_5 at temperatures greater than 100 °C; a similarly rapid decomposition occurred with thionyl chloride at 60 °C, apparently as a result of a von Braun degradation caused by nucleophilic attack by chloride ion at C-1, followed by rapid polymerization of the resulting 1-chloroisoquinoline under the reaction conditions. However, treatment of 1-benzamidoisoquinoline with thionyl chloride at 0 °C, followed by evaporation of the excess thionyl chloride and addition of sodium azide in DMF, gave the tetrazole **4** in 71% yield.

The 5-aryl-1-tetrazolyl substituents in the above model systems proved unexpectedly resistant to nucleophilic displacement. Thus, although **1** was converted to 4-ethoxypyridine in 81% yield with sodium ethoxide under reflux for 15 h and to 4-butylthiopyridine in 84% yield under similarly drastic conditions, it was inert to attempted displacement by sodium acetoacetate, sodium cyanide, butyllithium, butylmagnesium iodide, lithium acetonitrile, and sodium thiophenolate. Surprisingly, 4-[5-(*p*-nitrophenyl)-1-tetrazolyl]pyridine (**2**) was even less reactive; attempted displacement of the tetrazolyl grouping with sodium ethoxide, for example, led to a deep red reaction mixture from which an uncharacterized viscous red oil was the only isolated product. 2-(5-Phenyl-1-tetrazolyl)-pyridine (**3**) proved to be unreactive to all of the above nucleophiles. 1-(5-Phenyl-1-tetrazolyl)isoquinoline (**4**) reacted (albeit only under vigorous conditions) with ethoxide and butyl mercaptide anions to give the corresponding displacement products in good yields and gave 1-ethylisoquinoline by reaction with the Wittig reagent generated from ethyltriphenylphosphonium bromide and butyllithium followed by basic hydrolysis (28% overall yield), but it also proved to be inert to the other nucleophiles listed above.

The surprising unreactivity of the above 5-aryl-1-tetrazolyl substituents toward nucleophilic displacement led us to examine an alternative approach for the conversion of primary amino groups into potentially displaceable pendant heterocycles. A few years ago van Leusen and collaborators discovered that condensation of tosylmethyl isocyanide (TosMIC) with imidoyl chlorides led to 1,5-disubstituted 4-tosylimidazoles, while reaction with aldimines gave 1,5-disubstituted imidazoles.[6] In view of the excellent leaving group properties of imidazole itself,[7] it occurred to us that this synthetic concept might be utilized for the conversion of such substituent primary amino groups into derivatives capable of facile nucleophilic displacement. Modification of the van Leusen methodology was necessary, however, since (a) the greatly diminished nucleophilicity of heterocyclic amino groups makes aldimine formation difficult, (b) benzoylation of such amino groups, followed by treatment with phosphorus oxychloride or thionyl chloride, proved in our hands (vide supra) not to be a generally applicable route to imidoyl chlorides, and (c) the presence of a 5-substituent on the imidazole ring (a concomitant of both of the above synthetic procedures) would be anticipated to hinder the projected nucleophilic displacement reaction. We have found that ethoxymethylene derivatives of primary amino-substituted heterocycles **5** (which are readily available by reaction of the latter with triethyl orthoformate in the presence of *p*-toluenesulfonic acid) react smoothly with TosMIC at room temperature or below in dry DME in the presence of 1 equiv of sodium hydride to give 1-substituted 4-tosylimidazoles (**6**), with incorporation of the nitrogen of the

(1) This work was supported in part by a grant to Princeton University (Grant No. 5 RO1 GM27983) from the National Institutes of Health.
(2) National Institutes of Health Postdoctoral Fellow (Grant No. CA-05017).
(3) Sammes, P. G., Ed. "Comprehensive Organic Chemistry"; Pergamon Press: Oxford, 1979; Vol. 4.
(4) Butler, R. N. *Chem. Rev.* **1975**, *75*, 241–257.
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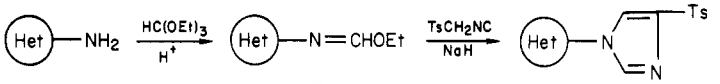
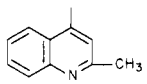
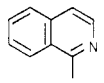
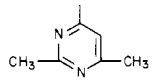
(6) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153–1159.
(7) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351–367.

Table I. Preparation and Reactions of 1-Substituted 4-Tosylimidazoles (6)



5 6

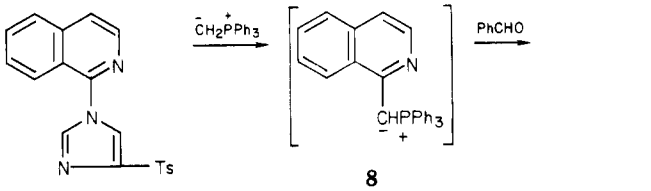
Het	% yield of 6 from 5	% yield of displacement product from 6 by NaOEt	$NaSC_4H_9$-n	NaSPh	$LiHBEt_3$
	90	83	74	*b*	*a*
	88	87	71	89	50
	75	92	62	74	30
	87	85	64	67	*a*

[a] Reaction occurred, but the desired product was not obtained in significant yield. [b] No reaction.

primary substituent amino group into N-1 of the imidazole ring. Representative transformations are given in Table I.

Nucleophilic displacement of the 1-(4-tosylimidazolyl) substituent is readily effected under mild conditions with sodium ethoxide, sodium *n*-butyl mercaptide, and sodium thiophenoxide (see Table I). The ease of displacement is underscored by our observation that initial attempts to condense TosMIC with the ethoxymethylene derivative of 4-aminoquinaldine at room temperature led to the formation in good yield of 4-ethoxyquinaldine by reaction of the intermediate 1-(4-tosylimidazolyl) substituent with the equivalent of sodium ethoxide released in the initial cycloaddition reaction. This in situ displacement could be avoided, however, when the condensation reaction was carried out at −25 °C. We were unsuccessful in attempts to effect analogous displacements with amines, cyanide ion, sodium phenylacetylide or diethyl sodiomalonate.

As anticipated, the 1-(4-tosylimidazolyl) substituent is also capable of displacement by strongly nucleophilic carbanions. 1-(1-Isoquinolinyl)-4-tosylimidazole (7), for



7 8 9

example, reacts smoothly with 3 equiv of methylenetriphenylphosphorane to give the new Wittig reagent 8, which was converted to 1-styrylisoquinoline (9) in 69% overall yield by reaction with benzaldehyde. The 1-(4-tosylimidazolyl) substituent appears to be approximately comparable to halogen in its ease of displacement by phosphorus ylides.[8]

The 1-(4-tosylimidazolyl) group can also be replaced by hydrogen. Thus, treatment of 1-(2-methyl-4-quinolinyl)-4-tosylimidazole with lithium triethylborohydride ("Super Hydride") gives quinaldine in 50% yield. An analogous transformation attempted with 1-(1-isoquinolinyl)-4-tosylimidazole was complicated by overreduction; isoquinoline could, however, be isolated in reasonable (30%) yield by bubbling a stream of oxygen through the reaction mixture. In view of the known difficulties encountered in replacement of primary amino substituents by hydrogen in heterocyclic systems,[9] this latter transformation may be worthy of further study.

Experimental Section

4-[5-(*p*-Nitrophenyl)-1-tetrazolyl]pyridine (2). A mixture of 7.29 g (0.030 mol) of 4-(*p*-nitrobenzamido)pyridine[10] and 6.24 g (0.030 mol) of phosphorus pentachloride in a 100-mL round-bottomed flask connected through a drying tube to a water aspirator was heated at 150 °C for 30 min. The residual material in the flask was dissolved in 300 mL of DMF, and to the resulting solution was added 3.58 g (0.055 mol) of sodium azide. The reaction mixture was stirred at room temperature for 1 h, and water was then added slowly. The initially clear solution rapidly turned turbid, and a solid then precipitated which was collected by filtration, dried, and recrystallized from 2-propanol to give 6.4 g (80%) of **2** as a colorless, crystalline solid, mp 183–184 °C.

Anal. Calcd for $C_{12}H_8N_6O_2$: C, 53.73; H, 3.01; N, 31.33. Found: C, 53.47; H, 3.14; N, 31.05.

2-(5-Phenyltetrazolyl)pyridine (3) was prepared in 48% yield from 3.96 g (0.020 mol) of 2-benzamidopyridine[11] and 4.16 g (0.020 mol) of phosphorus pentachloride as described above for the preparation of **2**; mp 98–100 °C (from 2-propanol).

Anal. Calcd for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.27; H, 3.95; N, 31.09.

1-(5-Phenyl-1-tetrazolyl)isoquinoline (4). To 60 g (0.5 mol) of thionyl chloride in a 250-mL flask cooled to 0 °C was added 22 g (0.09 mol) of 1-benzamidoisoquinoline,[12] and the resulting green solution was stirred at room temperature for 1 h and then evaporated to dryness. The residual solid was dissolved in 300 mL of DMF and the resulting solution added dropwise to a stirred mixture of 11.7 g (0.18 mol) of sodium azide in 60 mL of DMF.

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After the addition was complete (15 min), the mixture was stirred at room temperature for 45 min, cooled and diluted with 600 mL of water, and the solid which separated was collected by filtration, dried, and recrystallized from 900 mL of cyclohexane to give 17.4 g (71%) of a colorless crystalline solid, mp 104–105 °C.

Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.32; H, 4.06; N, 25.62. Found: C, 70.07; H, 4.27; N, 25.63.

Preparation of (Ethoxymethylene)amino Derivatives. General Procedure. A mixture of 0.1 mol of the amino heterocycle, 100 mL of triethyl orthoformate, and 0.25 g of *p*-toluenesulfonic acid was heated under reflux for 16 h and concentrated under reduced pressure, and the residue was triturated with ether. The solid which precipitated was removed by filtration and discarded; evaporation of the ether filtrate gave an oil which was purified by distillation under reduced pressure.

4-[(Ethoxymethylene)amino]pyridine: 55%; bp 69–70 °C (0.25 torr) [lit.[13] bp 63 °C (0.15 torr)]; NMR ($CDCl_3$) δ 1.17 (t, 3 H), 4.16 (q, 2 H), 6.70 (dd, 2 H), 7.57 (s, 1 H), 8.31 (dd, 2 H).

2-Methyl-4-[(ethoxymethylene)amino]quinoline: 88%; bp 120–122 °C (0.01 torr); NMR ($CDCl_3$) δ 1.14 (t, 3 H), 2.36 (s, 3 H), 4.17 (q, 2 H), 6.29 (s, 1 H), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.84; H, 6.41; N, 12.81.

1-[(Ethoxymethylene)amino]isoquinoline: 81%; bp 107 °C (0.01 torr); mp 32–34 °C; NMR ($CDCl_3$) δ 1.00 (t, 3 H), 4.12 (q, 2 H), 6.8–7.2 (m, 4 H), 7.7–8.2 (m, 3 H).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.72; H, 5.97; N, 14.16.

2,6-Dimethyl-4-[(ethoxymethylene)amino]pyrimidine: 40%; bp 84 °C (0.01 torr); mp 32–34 °C; NMR ($CDCl_3$) δ 1.21 (t, 3 H), 2.28 (s, 3 H), 2.47 (s, 3 H), 4.22 (q, 2 H), 6.50 (s, 1 H), 8.21 (s, 1 H).

Preparation of 1-Substituted 4-Tosylimidazoles. General Procedure. A mixture of 0.1 mol of TosMIC and 0.1 mol of the (ethoxymethylene)amino-substituted heterocycle in 100 mL of dry DME was added dropwise under nitrogen to a stirred slurry of 0.1 mol of sodium hydride in 40 mL of dry DME over a period of 20 min. The reaction mixture was stirred for 2 h at the temperature indicated below and poured into 1 L of water, and the precipitated product was collected by filtration.

1-(4-Pyridinyl)-4-tosylimidazole: 90% (at room temperature); mp 198–199 °C; NMR (Me_2SO-d_6) δ 2.20 (s, 3 H), 7.26 (d, 2 H), 7.6–7.9 (m, 4 H), 8.5–8.9 (m, 4 H).

Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04; S, 10.71. Found: C, 60.30; H, 4.33; N, 14.17; S, 10.64.

1-(2-Methyl-4-quinolinyl)-4-tosylimidazole: 88% (at room temperature; from benzene/cyclohexane); mp 219–220 °C; NMR ($CDCl_3$) δ 2.25 (s, 3 H), 2.65 (s, 3 H), 7.0–8.1 (m, 11 H).

Anal. Calcd for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56; S, 8.82. Found: C, 66.35; H, 4.50; N, 11.72; S, 9.15.

1-(1-Isoquinolinyl)-4-tosylimidazole: 75% (at −30 °C); mp 131–132 °C (from benzene/cyclohexane); NMR ($CDCl_3$) δ 2.32 (s, 3 H), 7.2–8.4 (m, 12 H).

Anal. Calcd for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.02; S, 9.18. Found: C, 65.50; H, 4.30; N, 11.78; S, 9.37.

1-(2,6-Dimethyl-4-pyrimidyl)-4-tosylimidazole: 87% (at −30 °C); mp 197–198 °C (from toluene); NMR ($CDCl_3$) δ 2.41 (s, 3 H), 2.68 (s, 3 H), 2.71 (s, 3 H), 7.37 (d + s, 3 H), 8.03 (d, 2 H), 8.51 (s, 2 H).

Anal. Calcd for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06; S, 9.76. Found: C, 58.77; H, 4.78; N, 17.19; S, 9.55.

Displacement of the 4-Tosylimidazolyl (or 5-Phenyl-1-tetrazolyl) Substituent by an Ethoxy Group. General Procedure. A mixture of 1-substituted 4-tosylimidazole (or 1-substituted 5-phenyltetrazole, 10 mmol), sodium ethoxide (12 mmol), and ethanol (25 mL) was heated under reflux for 6–12 h (completion of the reaction is readily monitored by TLC) and evaporated under reduced pressure, and the residue was dissolved in 30 mL of saturated sodium chloride. This solution was extracted with chloroform, and the chloroform extracts were dried and evaporated to give a residual oil which was distilled under reduced pressure.

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4-Ethoxypyridine: 83% (81% from 1); bp 105 °C (28 torr) [lit.[14] bp 94 °C (14 torr)]; NMR ($CDCl_3$) δ 1.15 (t, 3 H), 3.98 (q, 2 H), 6.70 (dd, 2 H), 8.32 (dd, 2 H).

4-Ethoxyquinaldine: 87%; mp 41–43.5 °C (lit.[15] mp 48 °C); NMR ($CDCl_3$) δ 1.29 (t, 3 H), 2.50 (s, 3 H), 3.92 (q, 2 H), 6.25 (s, 1 H), 7.0–8.1 (m, 4 H).

1-Ethoxyisoquinoline: 92% (82% from 4); mp (picrate) 156–157 °C (lit.[16] mp 158 °C).

2,6-Dimethyl-4-ethoxypyrimidine: 85%; bp 95 °C (30 torr) [lit.[17] bp 92–94 °C (35 torr)]; mp (picrate) 120–122 °C (lit.[17] mp 124–125 °C).

Displacement of the 4-Tosylimidazolyl (or 5-Phenyl-1-tetrazolyl) Substituent by an *n*-Butylthio Group. General Procedure. Sodium (0.115 g, 5 mmol) was dissolved in 10 mL of ethanol, and to this solution was added 0.55 g (6 mmol) of *n*-butyl mercaptan, followed by 3 mmol of the 1-substituted 4-tosylimidazole (or 1-substituted 5-phenyltetrazole) and 20 mL of ethanol. The mixture was either heated under reflux or stirred at room temperature, as indicated below. It was then concentrated under reduced pressure, the residue dissolved in 30 mL of saturated sodium chloride, and the aqueous solution extracted with chloroform. The extracts were dried and concentrated, and the residue was recrystallized or chromatographed.

4-(*n*-Butylthio)pyridine (reflux, 60 h): 74% (84% from 1); yellow oil; mp (picrate) 114–115 °C (lit.[18] mp 106–108 °C).

Anal. Calcd for $C_{15}H_{16}N_4O_7S$ (picrate): C, 45.45; H, 4.07; N, 14.14; S. 8.09. Found: C, 45.36; H, 4.04; N, 14.17; S, 7.88.

4-(*n*-Butylthio)quinaldine (reflux, 8 h): 71%; mp 68–69 °C (from hexane); NMR ($CDCl_3$) δ 0.8–2.0 (m, 7 H), 2.7 (s, 3 H), 3.05 (t, 2 H), 7.0 (s, 1 H), 7.2–8.2 (m, 4 H).

Anal. Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05; S, 13.86. Found: C, 72.76; H, 7.39; N, 5.87; S, 13.65.

1-(*n*-Butylthio)isoquinoline (reflux, 2.5 h): 62% (90% after 14 h from 4); oil (chromatographed on silica gel with chloroform); NMR ($CDCl_3$) δ 0.75 (t, 3 H), 1.0–1.8 (m, 4 H), 3.20 (t, 2 H), 6.98 (d, 1 H), 7.1–7.5 (m, 3 H), 7.7–8.0 (m, 1 H), 8.13 (d, 1 H).

Anal. Calcd for $C_{13}H_{15}NS$: C, 71.84; H, 6.96; N, 6.46; S, 14.75. Found: C, 72.06; H, 6.86; N, 6.63; S, 14.76.

2,6-Dimethyl-4-(*n*-butylthio)pyrimidine (room temperature): 64%; yellow oil (chromatographed on silical gel with chloroform); NMR ($CDCl_3$) δ 0.7–1.9 (m, 7 H), 2.25 (s, 3 H), 2.5 (s, 3 H), 3.1 (t, 2 H), 6.74 (s, 1 H).

Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.22; N, 14.27; S, 16.33. Found: C, 61.12; H, 8.55; N, 14.09; S, 16.28.

Displacement of the 4-Tosylimidazolyl Substituent by a Phenylthio Group. General Procedure. To a solution of sodium thiophenoxide in ethanol (prepared from 87.4 mg, 3.8 mmol, of sodium and 7 mL of ethanol) was added 3 mmol of the 1-substituted 4-tosylimidazole, and the mixture was heated under reflux for 16–84 h (monitored by TLC). The reaction mixture was worked up as described above for the sodium *n*-butyl mercaptide displacements.

4-(Phenylthio)quinaldine: 89%; mp 82–83 °C (from hexane); NMR ($CDCl_3$) δ 2.4 (s, 3 H), 6.6 (s, 1 H), 7.0–8.2 (m, 9 H).

Anal. Calcd for $C_{16}H_{13}NS$: C, 76.46; H, 5.21; N, 5.57; S, 12.76. Found: C, 76.60; H, 5.07; N, 5.37; S, 12.69.

1-(Phenylthio)isoquinoline: 75%; mp 57.5–59 °C (from petroleum ether) (lit.[19] mp 59–60 °C).

2,6-Dimethyl-4-(phenylthio)pyrimidine: 67%; mp 76–77 °C (from hexane); NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.6 (s, 3 H), 6.4 (s, 1 H), 7.2–7.8 (m, 5 H).

Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.83; H, 5.55; N, 12.80; S, 14.71.

Reduction of 1-(2-Methyl-4-quinolinyl)-4-tosylimidazole to Quinaldine with "Super Hydride". To 0.363 g (1 mmol) of 1-(2-methyl-4-quinolinyl)-4-tosylimidazole and 18 mL of dry

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DME in a 25-mL three-necked flask fitted with a 2 syrum stopper, drying tube, magnetic stirrer and nitrogen inlet was added, under nitrogen, 3 mL of 1 M "Super Hydride". The mixture was stirred under nitrogen for 1 h, poured into 50 mL of water, and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (preparative TLC, silica gel 60 F-254, 95:5 chloroform/ethyl acetate) to give 71 mg (50%) of quinaldine, identical in every respect with an authentic sample.

Under the same conditions, isoquinoline was obtained in 30% yield from (1-(1-isoquinolinyl)-4-tosylimidazole and "Super Hydride", except that oxygen was bubbled through the reaction mixture for 4 h prior to the workup.

Displacement of the 4-Tosylimidazolyl Substituent by a Wittig Reagent. Synthesis of 1-Styrylisoquinoline. Sodium hydride (50%, 0.192 g, 4 mmol), methyltriphenylphosphonium bromide (1.07 g, 3 mmol) and dry DME (40 mL) were added with stirring to a three-necked flask under nitrogen, and the mixture was heated under reflux for 2 h. To the cooled solution was then added 0.35 g (1 mmol) of 1-(1-isoquinolinyl)-4-tosylimidazole (under nitrogen), and the mixture was heated under reflux for 13 h. Benzaldehyde (0.6 g) was then added, and the mixture was heated under reflux for 12 h. It was then cooled and poured into 100 mL of water, and the aqueous solution was extracted with chloroform. The combined chloroform extracts were evaporated to dryness, the residue was dissolved in ether and filtered, and the filtrate was concentrated. Chromatography of the residue over silica gel with chloroform gave 150 mg (69%) of 1-styrylisoquinoline (mp 109–110 °C), identical in every respect with an authentic sample.

Displacement of the 5-Phenyl-1-tetrazolyl Substituent by a Wittig Reagent. Synthesis of 1-Ethylisoquinoline. To a stirred suspension of ethyltriphenylphosphonium iodide (4.6 g, 11 mmol) in 75 mL of dry DME under nitrogen at −40 °C was added 4.6 mL (11 mmol) of *n*-butyllithium (2.4 M). The reaction mixture was stirred for 2 h, and then a solution of 1.37 g (5.0 mmol) of **4** in 10 mL of dry DME was added. The reaction mixture was heated under reflux for 48 h and cooled, and a solution of 1.06 g (10 mmol) of sodium carbonate in 20 mL of water was added. The resulting solution was heated for 3 h under reflux and concentrated to a small volume under reduced pressure, and 50 mL of chloroform and 20 mL of saturated aqueous sodium chloride solution were added. The chloroform layer was separated and extracted with 5% aqueous HCl (4 × 50 mL). The combined acidic extracts were made alkaline with solid NaOH and extracted with ether (3 × 100 mL), and the combined ether extract was dried (Na_2SO_4) and evaporated to give a viscous oil. Distillation then gave 210 mg (28%) of 1-ethylisoquinoline as a colorless oil (picrate, mp 209–210 °C), identical with an authentic sample.

Registry No. **1**, 57761-77-0; **2**, 80781-06-2; **3**, 5454-05-7; **4**, 80781-07-3; **5** (Het = 4-pyridyl), 16705-92-3; **5** (Het = 2-methyl-4-quinolinyl), 80781-08-4; **5** (Het = 1-isoquinolinyl), 35257-15-9; **5** (Het = 2,6-dimethyl-4-pyrimidinyl), 80781-09-5; **6** (Het = 4-pyridyl), 80781-10-8; **6** (Het = 2-methyl-4-quinolinyl), 80781-11-9; **6** (Het = 1-isoquinolinyl), 80781-12-0; **6** (Het = 2,6-dimethyl-4-pyrimidinyl), 80781-13-1; **9**, 36680-19-0; 4-benzamidopyridine, 5221-44-3; 4-(*p*-nitrobenzamido)pyridine, 13160-58-2; sodium azide, 26628-22-8; 2-benzamidopyridine, 4589-12-2; 1-benzamidoisoquinoline, 33357-47-0; triethyl orthoformate, 122-51-0; 4-ethoxypyridine, 33399-46-1; 4-ethoxyquinaldine, 46272-56-4; 1-ethoxyisoquinoline, 66728-96-9; 1-ethoxyisoquinoline picrate, 80781-14-2; 2,6-dimethyl-4-ethoxypyridine, 4595-72-6; 2,6-dimethyl-4-ethoxypyridine picrate, 4679-06-5; 4-(*n*-butylthio)pyridine, 26891-64-5; 4-(*n*-butylthio)pyridine picrate, 53708-25-1; 4-(*n*-butylthio)quinaldine, 80781-15-3; 1-(*n*-butylthio)isoquinoline, 80781-16-4; 2,6-dimethyl-4-(*n*-butylthio)pyrimidine, 80781-17-5; 4-(phenylthio)quinaldine, 80781-18-6; 1-(phenylthio)isoquinoline, 19653-18-0; 2,6-dimethyl-4-(phenylthio)pyrimidine, 77752-56-8; quinaldine, 91-63-4; isoquinoline, 119-65-3; methyltriphenylphosphonium bromide, 1779-49-3; benzaldehyde, 100-52-7; ethyltriphenylphosphonium iodide, 4736-60-1; 1-ethylisoquinoline, 7661-60-1; 1-ethylisoquinoline picrate, 79172-39-7; 4-pyridinamine, 504-24-5; 4-amino-2-methylquinoline, 6628-04-2; 1-aminoisoquinoline, 1532-84-9; 4-amino-2,6-dimethylpyrimidine, 461-98-3; $TsCH_2NC$, 36635-61-7; NaOEt, 141-52-6; $NaSC_4H_9$-*n*, 4779-86-6; NaSPh, 930-69-8; $LiHBEt_3$, 22560-16-3.

Reactions at High Pressures. [3 + 2] Dipolar Cycloaddition of Nitrones with Vinyl Ethers†

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The [3 + 2] dipolar cycloaddition of a nitrone and an electron-rich depolarophile can be induced by high-pressure as well as by thermal reaction conditions, and the high-pressure conditions lead to altered stereoselectivities in the cycloaddition.

In recent years, the thermal [3 + 2] dipolar cycloaddition of nitrones with electron-deficient dipolarophiles (i.e., acrylates, styrenes, dienes, etc.) has been extensively utilized as a key feature in the total synthesis of structurally diverse natural products.[1] On the other hand, the synthetic potential offered by cycloadditions of nitrones and electron-rich olefins (i.e., vinyl ethers, enamines, etc.) has been neglected. Following the pioneering studies of Huisgen and his co-workers,[2] there has been limited research in this area of nitrone chemistry.[3] We viewed the cycloadduct (**5**) resulting from the dipolar cycloaddition of nitrone **1** and ethyl vinyl ether (**3**) as a masked β-amino aldehyde which could be released by reduction of the N,O bond and chose to incorporate this approach to β-amino aldehydes as a critical element in a synthetic project. Unfortunately, we were almost immediately confronted with a limitation to the approach: many nitrones are not

† This paper is dedicated to George Büchi on the occasion of his 60th birthday.

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