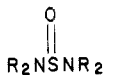
in cyclohexane) and the infrared stretching frequency of the C-H bond of PhC≡CH in the solvents (compared to the frequency in CCl_4).[14] The values for **4b** of -0.70 ppm and -55 cm^{-1} are much closer to those for sulfolane (-0.68 ppm and -47 cm^{-1}) than to those for HMPA (-2.03 ppm and -153 cm^{-1}) or even dimethyl sulfoxide (-1.34 ppm and -110 cm^{-1}). With respect to its E_T value, a parameter[15] related more to general solvent polarity than to specific solvating ability, **4b** (41.8 kcal/mol) is similar to sulfolane (44.0 kcal/mol). The dipole moment of **4a** (4.38 D)[16] is also similar to that of sulfolane (4.69 D).[17]

By analogy to comparisons[18] between sulfoxides and sulfones, sulfurous diamides (**5**) should have more polar



R_2NSNR_2

5a, R = Me

aprotic solvent character than do sulfamides. However, they would be expected to be considerably less stable toward nucleophilic and basic reagents. We found that a 2.5 M tetrahydrofuran solution of methylmagnesium chloride to which 1 equiv of **5a** was added had a half-life of about 2 h at ambient temperature.

One problem with (or virtue of) the use of sulfamides as solvents is their low water solubility. Unlike many polar aprotic solvents, **4a** and **4b** cannot be removed easily from typical organic materials by a few washes with water. As a result, applications that require separation of the solvent from other relatively water-insoluble compounds would necessitate distillation, chromatography, or repeated extraction with water. Of course, for some applications, low water solubility could be advantageous. There is also the possibility of constructing related molecules having greater water solubility.

Experimental Section

Tetraethylsulfamide (4b). The following procedure proved to be convenient.[19] A solution of sulfuryl chloride (76.6 mL, 0.946 mol) in pentane (100 mL) was added dropwise to a stirred solution of diethylamine (392 mL, 3.78 mol) in pentane (400 mL) that was cooled in an ice bath. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature. Additional diethylamine (100 mL) was added, and the mixture was refluxed for 6 h. The reaction mixture was filtered, and most of the pentane was removed from the filtrate at reduced pressure. The remaining filtrate was washed repeatedly with small portions of water and then distilled to give **4b**, bp 95-102 °C (1 torr). A Karl Fischer titration showed the water content to be less than 10^{-3} M.

Other Materials. Tetramethylsulfurous diamide (**5a**) was synthesized by using a procedure already reported.[20] The Grignard reagents were prepared by using freshly distilled organic halides and magnesium turnings (Johnson Matthey Chemicals, "Puratronic"). Solutions of diethylzinc, butyllithium, and methylmagnesium chloride were commercial samples (Alfa Products). The 4-(2,4,6-triphenylpyridinium)-2,6-diphenylphenoxide used to determine the E_T value was donated by Charles deBrosse (The Pennsylvania State University).

Preparation of Grignard Reagents in Tetraethylsulfamide (4b). Reactions were carried out in a standard-taper, three-necked, round-bottomed flask containing a magnetic stirring bar and fitted with a pressure-equalizing dropping funnel and a condenser having a gas-inlet tube at the top. Magnesium (0.53 g, 22 mmol) was added to the apparatus, and then the apparatus was heated gently with a heat gun while nitrogen flowed rapidly through it. During the course of a reaction, a slightly positive pressure of nitrogen was maintained in the closed reaction system. After the apparatus had cooled, the organic halide (20 mmol) and **4b** (20 mL) were added to the flask, and then the reaction mixture was stirred for 12 h. In the reaction with bromobenzene, a small amount of 1,2-dibromoethane was also added; in the absence of this additive, the Grignard reagent did not form appreciably.

Concentrations of Grignard reagents were determined by hydrolysis of aliquots followed by titration of the resulting base. Two preparations of ethylmagnesium bromide gave essentially identical yields, as did three preparations of propylmagnesium bromide. Essentially the same concentrations of one ethylmagnesium bromide and one propylmagnesium bromide preparation were found when a double-titration procedure[21] was used.

Acknowledgment. We are grateful to the National Science Foundation for support of this research and for aiding in the purchase of the NMR spectrometers that were used. We thank Charles DeBrosse for helpful suggestions.

Registry No. 4b, 2832-49-7.

(14) Agami, C.; Caillot, M. *Bull. Soc. Chim. Fr.* **1969**, 1990 and references cited therein. Taft's β would be a better measure: Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377; Kamlet, M. J.; Solomonovici, A.; Taft, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 3734.

(15) Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlmann, F. *Justus Liebigs Ann. Chem.* **1963**, *661*, 1. Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 29. Taft's π^* is a more recently developed measure: Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 6027; Abboud, J. L.; Kamlet, M. J.; Taft, R. W. *Ibid.* **1977**, *99*, 8325; Kamlet, M. J., Hall, T. N.; Boykin, J.; Taft, R. W. *J. Org. Chem.* **1979**, *44*, 2599.

(16) In benzene at 25 °C: Nöth, H.; Mikulaschek, G.; Rambeck, W. *Z. Anorg. Allg. Chem.* **1966**, *344*, 316.

(17) In benzene at 25 °C: Longster, G. F.; Walker, E. E. *Trans. Faraday Soc.* **1953**, *49*, 228. A value of 4.81 D has also been reported: Cumper, C. W. N.; Vogel, A. I. *J. Chem. Soc.* **1959**, 3521.

(18) For example, see: Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875.

(19) Procedures for synthesizing **4b** have already been described: Behrend, R. *Justus Liebigs Ann. Chem.* **1884**, *222*, 116; Denivelle, L. *Bull. Soc. Chim. Fr.* **1936**, [5] *3*, 2143; Roseky, H. W.; Hoff, A. *Chem. Ber.* 1965, *98*, 2429.

(20) Dorlars, A. "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Georg Thieme Verlag: Stuttgart, 1958; Vol. 11, Part 2, p 641.

(21) Vlismas, T.; Parker, R. D. *J. Organomet. Chem.* **1967**, *10*, 193.

One-Step Conversions of Esters to 2-Imidazolines, Benzimidazoles, and Benzothiazoles by Aluminum Organic Reagents

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Aluminum organic reagents play an increasingly important role in effecting simple chemical transformations. Several examples, recently published, include conversions of esters to thioesters,[1] ketene thioacetals,[2] and amides,[3] of esters to nitriles,[4] and of epoxides to amino alcohols.[5]

(1) (a) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **95** 5830 (1973); (b) R. P. Hatch and S. M. Weinreb, *J. Org. Chem.*, **42**, 3960 (1977); (c) T. Cohen and R. E. Gapinski, *Tetrahedron Lett.*, 4319 (1978); (d) T. Cohen and R. E. Gapinski, and R. R. Hutchins, *J. Org. Chem.*, **44**, 3599 (1979).

(2) E. J. Corey and A. P. Kozikowski, *Tetrahedron Lett.*, 925 (1975).

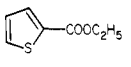
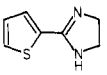
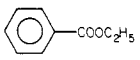
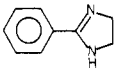
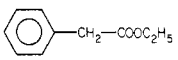
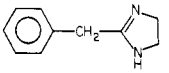
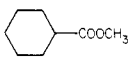
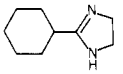
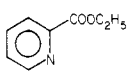
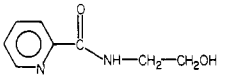
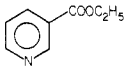
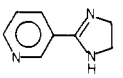
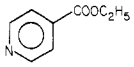
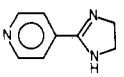
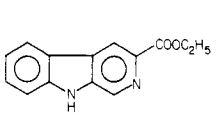
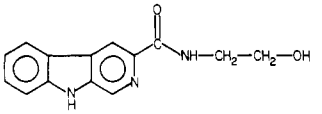
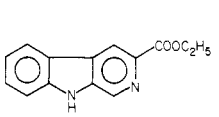
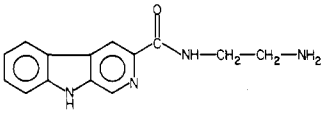
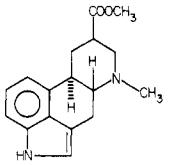
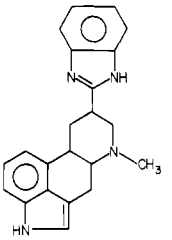
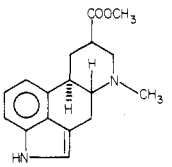
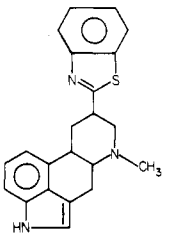
(3) A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 4171 (1977).

(4) J. L. Wood, N. A. Khatri, and S. M. Weinreb, *Tetrahedron Lett.*, 4907 (1979).

(5) L. E. Overman and L. A. Flippin, *Tetrahedron Lett.*, 195 (1981).

0022-3263/81/1946-2824$01.25/0

Table I. Representative Examples

educt	product[a,b]	% yield	mp, °C (lit. mp, °C)
		92	178-180 (175-177[10])
		93	96-98 (101[11])
		89	65-68 (66-68[11])
		96	129-132
		72	bp 160 (1 mm) [bp[12] 167 (1.6 mm)]
		90	106-107 (111[11])
		91	136-137 (136-137.3[13])
		83	224-227
		82	178-180
		56[c,e]	182-185
		58[c,e]	196-198

[a] All compounds were characterized by ^{1}H NMR and IR spectra as well as elemental analysis; data are available on request from the authors. [b] Reaction conditions and molar ratios were as described in the experimental section. [c] 23% open-chain amide as byproduct. [d] 28% amide as byproduct. [e] The respective yields could be improved (72% and 75%) by doubling the reaction time and the amount of aluminum organic reagent.

In comparison with older standard procedures reagents of the type R_2AlX (X = NR_2, SR) generally offer the advantage of broad applicability and of mild reaction conditions.

In this note we report that bifunctional units such as 1,2-diaminoethane, 1,2-diaminobenzene, and 2-mercaptoaniline are effectively coupled with trimethylaluminum to produce reagents[6] that can be treated with a wide variety of esters to give 2-imidazolines, benzimidazoles, and benzothiazoles, respectively.

Conventional preparation of 2-imidazolines normally requires nitriles or imino ethers as starting materials. Only in selected cases can carboxylic acid esters be reacted directly with ethylenediamine to give 2-imidazolines. Drastic reaction conditions (sealed tube, 160–300 °C) often limit the usefulness of these procedures.[7] Direct formation of benzimidazoles[8] and benzothiazoles[9] from esters suffers from similar limitations.

(6) The constitution of the reactive aluminum organic compound is formally given as $R_2AlNHCH_2CH_2NH_2$, although monomeric species of that type are quite improbable to exist in solution; the true nature of the reagent remains to be investigated.

(7) (a) R. J. Ferm and J. L. Riebsamer, *Chem. Rev.*, **54**, 593 (1954); (b) V. B. Piskov, V. P. Kasperovich, and L. M. Yakovleva, *Khim. Geterotsikl. Soedin.*, 1112 (1976); *Chem. Abstr.*, **86**, 5372 (1977).

(8) P. N. Preston, *Chem. Rev.*, **74**, 297 (1974); J. B. Wright, *Chem. Rev.*, **48**, 397 (1951).

(9) F. Kurzer, *Org. Compd. Sulphur, Selenium, Tellurium*, **2**, 653 (1973); *ibid.*, **3**, 617 (1975); B. Iddon and P. A. Lowe, *ibid.*, **4**, 386 (1977).

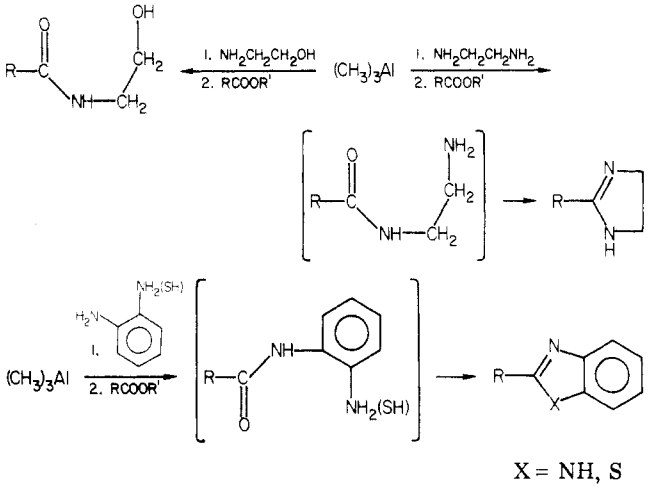
(10) B. George and E. P. Papadopoulos, *J. Org. Chem.*, **42**, 441 (1977).

(11) P. Oxley and W. F. Short, *J. Chem. Soc.*, 497 (1947).

(12) E. E. Glover and M. J. R. Loadman, *J. Chem. Soc. C*, 2391 (1967).

(13) M. Harfenist, F. E. Soroko, and G. M. McKenzie, *J. Med. Chem.*, **21**, 405 (1978).

Scheme I



X = NH, S

Table I shows that a wide range of esters is easily transformed according to Scheme I. Some limitations, however, must be mentioned; reaction of dimethylaluminum 2-hydroxyethylamide fails to produce the expected oxazolines, instead quantitative formation of 2-hydroxyethylamides is observed. In the cases of vicinal diamines and amino thiols, ring closure is favored although sometimes prolonged reaction times and excess aluminum organic reagent may be necessary to avoid mixtures of open-chain amides and ring-closed heterocycles. Neighboring group interference is observed in the cases of β-carboline-3-carboxylates and 2-picolinates; their conversion generally stops at the amide stage, so that formation of the corresponding heterocycles requires a separate dehydration step using conventional methodology.[7]

As a control experiment the esters listed in Table I were refluxed in toluene in the presence of 10 mol equiv of ethylenediamine. After 10 h at reflux temperature they were recovered almost unchanged, thin-layer chromatography showing only traces of reaction products.

Experimental Section

Typical Example. Ethylenediamine (3.91 mL, 0.058 mol) is added dropwise to a stirred solution of trimethylaluminum (0.058 mol) in 50 mL of toluene, so that the temperature does not exceed 10 °C. At the end of methane evolution ethyl thiophene-2-carboxylate (5.7 g, 0.036 mol) is gradually added at room temperature. The reaction mixture is refluxed for 3 h (argon atmosphere). After cooling, the solution is treated dropwise with 15 mL of water, diluted with 50 mL of methanol and 50 mL of methylene chloride, and refluxed on a steam bath for 15 min. After filtration over Na_2SO_4 and solvent evaporation the residue is suspended in 200 mL of ethyl acetate and refluxed for another 15 min in order to remove traces of aluminum hydroxides from the crude product. Filtration of the hot solution over Na_2SO_4 and removal of the solvent in vacuo followed by recrystallization of the crude product from ethyl acetate results in pure 2-(2-thienyl)-2-imidazoline: 5.1 g (92% yield); mp 178–180 °C; ^1H NMR (Bruker HX 90, Me_2SO-d_6) δ 3.60 (s, 4 H), 7.12 (dd, J = 5.0, 3.8 Hz, 1 H), 7.52 (dd, J = 3.8, 1.2 Hz, 1 H), 7.64 (dd, J = 5.0, 1.2 Hz, 1 H); IR (KBr) 3140 (NH), 2930 and 2850 (CH), 1600 (C=N) cm^{-1}.

Acknowledgment. We are much indebted to Dr. K. H. Müller of Schering AG Bergkamen for a generous gift of trimethylaluminum.

Registry No. Ethyl thiophene-2-carboxylate, 2810-04-0; ethyl benzoate, 93-89-0; ethyl phenylacetate, 101-97-3; methyl cyclohexanecarboxylate, 4630-82-4; ethyl picolinate, 2524-52-9; ethyl nicotinate, 614-18-6; ethyl isonicotinate, 1570-45-2; ethyl β-carboline-3-carboxylate, 74214-62-3; methyl 6-methyl-8β-ergolinecarboxylate, 35470-53-2; 2-(2-thienyl)-2-imidazoline, 45753-18-2; 2-phenyl-2-imidazoline, 936-49-2; 2-benzyl-2-imidazoline, 59-98-3; 2-cyclohexyl-2-imidazoline, 67277-65-0; *N*-(2-hydroxyethyl)picolinamide, 16347-06-1; 2-(3-pyridinyl)-2-imidazoline, 6302-53-0; 2-(4-pyridinyl)-2-imidazoline, 21381-61-3; 2-[(β-carbolin-3-yl)carbonylamino]ethanol, 77415-47-5; *N*-[(β-carbolin-3-yl)carbonyl]ethylenediamine, 77415-48-6; 8β-(2-benzimidazolin-2-yl)-6-methylergoline, 77429-52-8; 8β-(2-benzothiazolin-2-yl)-6-methylergoline, 77429-53-9; *N*-[(6-methylergolin-8β-yl)carbonyl]-*o*-phenylenediamine, 77415-49-7; *o*-[(6-methylergolin-8β-yl)carbonylamino]benzenethiol, 77415-50-0; ethylenediamine, 107-15-3; 1,2-diaminobenzene, 95-54-5; 2-mercaptoaniline, 137-07-5; 2-aminoethanol, 141-43-5; trimethylaluminum, 75-24-1.

Communications

Total Synthesis of (±)-4′-Demethyl-4-epipodophyllotoxin by Insertion–Cyclization

Summary: The total synthesis of (±)-4′-*O*-demethyl-4-epipodophyllotoxin (**3**) is accomplished in 13 steps and 2.4% overall yield from piperonal through the use of an "insertion–cyclization" reaction to form the aryltetralin ring system.

Sir: The development of the glycosidic lignan lactones etoposide (1)[1] and teniposide (2)[1] into major clinical agents against lung and bladder cancer[2] has spurred recent interest in the efficient total synthesis of their common aglycon, 4′-*O*-demethyl-4-epipodophyllotoxin (3).[3] Despite the pioneering synthesis of podophyllotoxin (4) by Gensler and his school,[4] and the very recent studies by Murphy[5] and Rodrigo,[6] no practical laboratory synthesis of these lignan lactones exists. We now report successful implementation of a new strategy for this purpose.

Our strategy exploits the principle of insertion–cyclization, whereby a slow cyclization between nucleophilic (N) and electrophilic (E) termini of a molecular array can be intercepted by insertion of a reactive moiety U which

(1) Keller-Juslén, C.; Kuhn, M.; von Wartburg, A.; Stähelin, H. *J. Med. Chem.* **1971**, *14*, 936.

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(3) Kuhn, M.; Keller-Juslén, C.; von Wartburg, A. *Helv. Chim. Acta* **1969**, *52*, 944.

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