in the reactor flask by addition of 21 mL (21 mmol) of a 1 M solution of ethanolic sodium borohydride stabilized with sodium hydroxide to a magnetically stirred suspension of 5.28 g (21 mmol) of nickel(II) acetate tetrahydrate in 170 mL of 95% ethanol. After 3 min hydrogen evolution ceased, and 2.84 mL (2.55 g, 42 mmol) of ethylenediamine was added as a catalyst poison.[4] To the resulting black suspension was added 9.0 g (84.8 mmol) of 2,6-octadiyne (3). Hydrogen uptake commenced immediately. After 3 h hydrogen uptake ceased, and 2 g of decolorizing carbon was added to the reaction mixture, which was then filtered through a Celite pad. The purple filtrate was diluted with 450 mL of water, and the product was isolated by pentane extraction and distillation to afford 7.30 g (78%) of (*Z,Z*)-2,6-octadiene (5) as a colorless liquid: bp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 6 H, RCH_3), 2.07 (m, 4 H, RCH_2CH_2R), 5.43 (m, 4 H, RCH=CHR); ^{13}C NMR ($CDCl_3$) δ 12.81, 26.94, 124.11, 130.18; IR (neat) 1650, 1440, 1400, 1365, 710 cm^{-1}, identical with that reported in the literature.[2a] Inspection of the ^{1}H and ^{13}C NMR spectra of diene 5 prepared in this manner shows the presence of ~5% of *cis*-2-octene. For our study,[1] that required stereochemical purity, this material was quite satisfactory. However, the diene was readily separated from octene by chromatography on silica gel impregnated with 10% by weight of silver nitrate. Thus, 1 g of distilled product was chromatographed through 100 g of silver nitrate–silica gel. Elution with 500 mL of pentane and then 400 mL of 10% ether/pentane gave a small amount of (*Z*)-2-octene, identified by its ^{1}H NMR. Elution with 400 mL of ether, followed by distillation, gave 270 mg (27%) of (*Z,Z*)-2,6-octadiene (5) that contained no trace of 2-octene by ^{1}H NMR.

(*E,E*)-2,6-Octadiene (6). To a mechanically stirred solution of 11.0 g (480 mmol) of sodium metal in dry liquid ammonia was added a solution of 8.5 g (80 mmol) of 2,6-octadiyne (3) in 20 mL of dry THF. After 30 min the reaction was quenched by careful addition of 26 g (480 mmol) of ammonia chloride, and most of the ammonia was allowed to evaporate slowly through a glass helices packed column with a slow stream of argon. The resulting slurry was diluted with 400 mL of water, and the product was isolated by pentane extraction and distillation to give 6.72 g (71%) of (*E,E*)-2,6-octadiene (6) as the only pentane-soluble product: colorless liquid; bp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 6 H, RCH_3), 2.02 (br s, 4 H, RCH_2CH_2R), 5.42 (m, 4 H, RCH=CHR); ^{13}C NMR ($CDCl_3$) δ 17.91, 32.76, 124.89, 131.00; IR (neat) 1440, 1378, 962 cm^{-1}, identical with that reported in the literature.[2a]

(*E*)-2-Octen-6-yne (4). Dry ammonia (200 mL) was distilled into a flask containing 1.67 g (70 mmol) of oil-free sodium hydride. Mechanical stirring was commenced, and the gray suspension was cooled with a bath at −60 °C (dry ice/2-propanol). After 30 min a solution of 4.0 g (43.4 mmol) of 1,5-heptadiyne (2) in 1 mL of dry THF was added, dropwise, via syringe. After an additional 30 min 2.99 g (130 mmol) of sodium metal was added in small pieces. The resulting blue solution was stirred for 20 min, and then 14.6 mL (33.3 g, 235 mmol) of dry methyl iodide was added dropwise. The solution decolorized to a white suspension immediately upon addition of the first few drops of methyl iodide. After an additional 20 min at −60 °C the reaction mixture was allowed to warm slowly to the boiling point of ammonia. Evaporation of most of the ammonia with a slow stream of argon, dilution of the resulting slurry with 200 mL of water, and isolation of the product by pentane extraction and simple vacuum distillation afforded 3.14 g of crude product, bp 85–87 °C (150 mm). The ^{1}H NMR spectrum of the material obtained in this manner revealed that the desired product was ~90% pure (60% yield of enyne 4). The only impurities were THF and 1,5-heptadiene. This crude product was used for the preparation of (*E,Z*)-2,6-octadiene as described below. Refractionation of an aliquot of the crude product through a Vigreux column gave analytically pure (*E*)-2-octen-6-yne (4): colorless liquid; bp 85–87 °C (150 mm); ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 3 H, R=CHCH$_3$), 1.78 (br s, 3 H, R≡CCH$_3$), 2.17 (m, 4 H, RCH_2CH_2R), 5.53 (m, 2 H, RCH=CHR); IR (neat) 3005, 2980, 2900, 2840, 1450, 1435, 965 cm^{-1}. Anal. Calcd for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.45; H, 11.28.

(*E,Z*)-2,6-Octadiene (7). (*E*)-2-Octen-6-yne (4; 2.30 g of material ~90% pure by NMR, 2.1 g of enyne, 19.4 mmol) was hydrogenated by using the procedure described above for the preparation of (*Z,Z*)-2,6-octadiene (5) and utilizing 0.44 g (1.77 mmol) of $Ni(OAc)_2 \cdot 4H_2O$ and 0.30 mL (0.27 g, 4.42 mmol) of ethylenediamine for generation of the catalyst. Extractive workup and distillation afforded 1.38 g (65%) of (*E,Z*)-2,6-octadiene (7): colorless liquid; bp 116–120 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (m, 6 H, RCH_3), 2.06 (br s, 4 H, RCH_2CH_2R), 5.42 (m, 4 H, RCH=CHR); ^{13}C NMR ($CDCl_3$) δ 12.77, 17.91, 27.04, 32.57, 123.91, 124.98, 130.13, 131.00; IR (neat) 1650 (w), 1440, 905, 700 cm^{-1}, identical with that reported in the literature.[2a] The ^{1}H and ^{13}C spectra of diene 7 prepared in this manner show the presence of ~5% of a mixture of (*E*)- and (*Z*)-2-octene.

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Registry No. 1, 628-16-0; 2, 764-56-7; 3, 764-73-8; 4, 73368-54-4; 5, 18680-11-0; 6, 18152-31-3; 7, 18152-32-4; (*Z*)-2-octene, 7642-04-8; (*E*)-2-octene, 13389-42-9.

(11) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226–30.

Reaction of α-Amino Ketone Hydrochlorides with Ortho Esters: An Oxazole Synthesis

John L. LaMattina

Central Research, Pfizer Inc., Groton, Connecticut 06340

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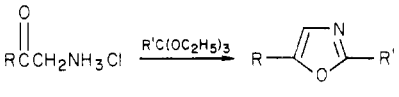
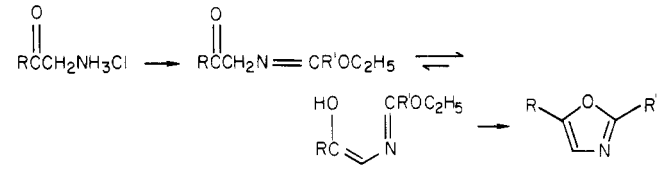
The synthesis of oxazoles by a variety of methods has recently been extensively reviewed.[1,2] Among these methods, the conceptually facile reaction of α-amino ketone hydrochlorides with ortho esters has received scant attention and, in fact, only one example of this reaction has been reported.[3] The work described herein demonstrates this approach to be both simple and general, thereby providing a variety of 2,5-disubstituted oxazoles from readily available α-amino ketone hydrochlorides.[4] The results are summarized in Table I.



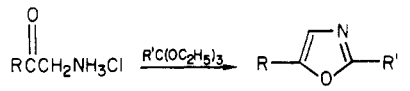
It should be noted that substrates 1, 5, and 7 all react more rapidly than 3. This is apparently due to the ability of these substrates to more easily undergo enolization and subsequent cyclization, since the initial imino ether formation is quite rapid (<0.25 h) for all substrates. It would appear then that this procedure is limited to α-amino ketone hydrochlorides in which the R group is electron deficient.



(1) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.
(2) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99.
(3) Demchenko, N. P.; Grekov, A. P. *Zh. Obshch. Khim.* **1962**, *32*, 1219; *Chem. Abstr.* **1963**, *58*, 14431.
(4) The method employed for the synthesis of the α-amino ketone hydrochlorides used in this work is that of: Clemo, G.; Holmes, L.; Leitch, G. *J. Chem. Soc.* **1938**, 753. NMR analysis of the crude α-amino ketone hydrochlorides showed that they were >95% pure, and they were used without further purification.
(5) Gabriel, S. *Ber.* **1910**, *43*, 1283.

0022-3263/80/1945-2261$01.00/0

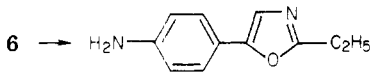
Table I[b]



substrate	product	yield,[a] %	reacn time, h	mp/bp, °C
1, R = 4-pyridyl·HCl	2a, R′ = H	58	2	120-121 (cyclohexane)
	2b, R′ = CH_3	59	2	76-77 (petroleum ether)
	2c, R′ = C_2H_5	79	2	90 (0.1 torr)
3, R = phenyl	4a, R′ = H	33	16	40-41
	4b, R′ = CH_3	41	16	57-58[5]
	4c, R′ = C_2H_5	60	16	94 (0.5 torr)
5, R = *p*-nitrophenyl	6, R′ = C_2H_5	68	2	85-86 (cyclohexane)
7, R = *p*-bromophenyl	8, R′ = H	48	7	66-67 (hexane)

[a] Refers to the amount of pure product isolated. [b] Satisfactory analytical data were reported for all new compounds.

However, considerable synthetic flexibility exists once the oxazole is formed. Thus, *p*-nitrophenyl oxazole **6** can



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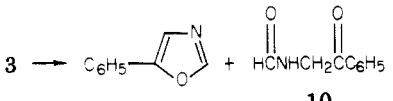
be readily reduced to the corresponding anilino derivative (**9**) in 94% yield by catalytic hydrogenation. Subsequent conversions of aromatic amino moieties are well documented, and so a wide variety of other derivatives are potentially available, including those where R is electron rich.

The low yield obtained in the synthesis of **4a** is some-

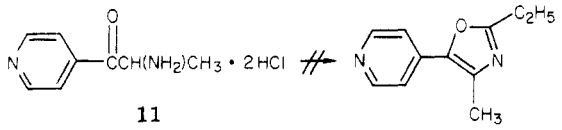


4a **10**

what puzzling, especially in light of the 60% yield reported by previous investigators.[3] In fact, the major product of this reaction is formamide derivative **10**. This material, which appears to result from hydrolytic workup of the uncyclized intermediates, can be isolated in yields of ~45%. The discrepancy between these results and those previously reported is not understood.

The data in Table I reveal that higher-boiling ortho esters afford higher product yields. Attempts were therefore made to improve the yield of **4a** by using mesitylene (bp 162-164 °C) as the solvent with 2.5 equiv of triethyl orthoformate as reagent and *p*-TsOH as catalyst. In this case only 21% of **4a** was isolated. Another attempt to increase the yield of **4a** involved the use of acetic acid as solvent and catalyst in the hopes of facilitating enol formation. Again, 2.5 equiv of triethyl orthoformate were used. Although **4a** could by obtained in this way, the yield (31%) offered no advantage to the standard method. Other parameters were also varied to no avail.

Although this reaction is successful for the synthesis of 2,5-disubstituted oxazoles, it does not appear applicable to 2,4,5-trisubstituted oxazoles, since reaction of **11** with triethyl orthopropionate gave multiple products.



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This approach to oxazoles has the advantage that it is a one-pot procedure and thus does not involve two separate steps as does the classical Robinson–Gabriel synthesis. Furthermore, this method is successful for α-amino ketone hydrochlorides which contain amino heterocycle moieties, substrates for which the Robinson–Gabriel synthesis is unsuccessful.[6]

Although seemingly little utilized, the reaction of α-amino ketone hydrochlorides with triethyl ortho esters is a viable method for the synthesis of a wide variety of 2,5-substituted and 5-monosubstituted oxazoles. The procedure is simple, makes use of readily available materials, nicely complements other recent oxazole syntheses,[7] and offers an alternative to the classical Robinson–Gabriel synthesis.

Experimental Section

General Procedure. A mixture of 20 mmol of the α-amino ketone hydrochloride,[4] 100 mg of *p*-toluenesulfonic acid,[8] and 60 mL of the triethyl ortho ester[9] was heated in a 125-mL round-bottomed flask until the internal temperature of the reaction mixture reaches 140 °C. (This allowed the ethanol which was generated to boil away.) A reflux condenser was fitted to the flask and the mixture was heated at reflux until TLC showed that the substrate had been consumed (see Table I). The mixture was then distilled through a 4-cm Vigreux column under reduced pressure (40 mmHg) to remove the excess ortho ester, and the residue was taken up into 50 mL of toluene. The mixture was extracted with three 25-mL portions of 6 M HCl (1 M HCl was used if the substrate was **1**). The combined acid extracts were made basic with solid Na_2CO_3, and the aqueous mixture was extracted three times with a total of 75 mL of $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and evaporated, leaving the product which was purified as indicated in Table I.

5-Phenyloxazole (4a) was purified by chromatography over silica gel, using isopropyl ether as eluant to afford white crystals, mp 40–41 °C (lit.[3] mp 40 °C). Further elution with $CHCl_3$ afforded amide **10**, recrystallized from toluene, mp 80–81.5 °C. Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.55; N, 8.58. Found: C, 65.95; H, 5.53; N, 8.52.

2-Ethyl-5-(4-anilino)oxazole (9). A mixture of 1.00 g (4.58 mmol) of **6**, 100 mg of 10% Pd/C, and 50 mL of absolute EtOH was hydrogenated at room temperature and 3-atm pressure. On completion of the reduction, the mixture was filtered to remove the catalyst and then concentrated to leave a white solid. Recrystallization from toluene/cyclohexane afforded 0.81 g (94%) of **9**, mp 118–119 °C. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.05; H, 5.99; N, 14.73.

Registry No. **1**, 73286-33-6; **2a**, 70380-75-5; **2b**, 23899-36-7; **2c**, 73286-34-7; **3**, 5468-37-1; **4a**, 1006-67-3; **4b**, 3969-09-3; **4c**, 69163-81-1; **5**, 5425-81-0; **6**, 73286-35-8; **7**, 5467-72-1; **8**, 7064-31-5; **9**, 73286-36-9; **10**, 73286-37-0; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7; triethyl orthopropionate, 115-80-0.

(6) LaMattina, J. L., unpublished observations.
(7) (a) Doyle, M. P.; Oppenhuizen, M.; Elliot, R. C.; Boelkins, M. R. *Tetrahedron Lett.* **1978**, 2247. (b) Ibata, T.; Sato, R. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3597.
(8) When **1** is the substrate, *p*-TsOH is not necessary.
(9) The use of trimethyl ortho esters results in much slower reactions, presumably due to the lower-boiling nature of these reagents.