(83%): NMR ($CDCl_3$) δ 0.10 (s, 6), 0.90 (s, 9), 1.26 (d, 3, J = 6.5 Hz), 1.30 (d, 3, J = 7 Hz), 2.40-2.76 (m, 1), 2.82 (dm, 1, J = 5.5 Hz, H-3), 3.72 (dd, 1, J = 9, 2 Hz, H-4), 4.22 (quint, 1, J = 6.5 Hz, H-3a), 6.64 (br, 1). Esterification of acid **13** with excess diazomethane gave the crystalline methyl ester **14** which is identical in all respect with that reported by Merck.[23]

Acknowledgment. We thank our co-workers T. Hawlicek, H. Knapp, E. Satzer, and K. Wagner for their diligent technical assistance and Dr. G. Schulz and his staff for the spectroscopic analyses.

Registry No. **5a**, 97403-52-6; **5b**, 97403-53-7; **5c** (isomer 1), 97403-54-8; **5c** (isomer 2), 97466-02-9; **5d**, 97415-93-5; **5e**, 97465-99-1; **5f**, 97403-55-9; **5g**, 97403-56-0; **5i**, 97403-61-7; **5k**, 97403-62-8; **6a**, 76855-69-1; **6b**, 85768-10-1; **6e**, 96855-25-3; **7d**, 97415-94-6; **8**, 24850-33-7; **9**, 31197-41-8; **10a**, 97403-57-1; **10b**, 97403-58-2; **10c**, 97466-00-7; **11b**, 96613-71-7; **11c**, 96543-02-1; **12a**, 97403-59-3; **12b**, 97403-60-6; **12c**, 97466-01-8; **13**, 97101-07-0; **14**, 87037-96-5; EtSH, 75-08-1.

Reaction of Ketone Enolates with 2,4-Dichloropyrimidine. A Novel Pyrimidine to Pyridine Interconversion[1a]

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Treatment of 2,4-dichloropyrimidine (**1**) with a series of ketone potassium enolates in liquid NH_3 results in a novel ring transformation leading to the formation of 6-(cyanamino)pyridines (**8a-c**). An S_N(ANRORC) mechanism initiated by nucleophilic addition of the enolate to C_6 of **1** is proposed. The pyrimidine–pyridine transformation involves displacement of the N_1–C_2–N_3 portion of pyrimidine with a C–C–N moiety, where the enolate contributes the C–C fragment while NH_3 is shown, using ^{15}N-labeled NH_3, to be the N donor.

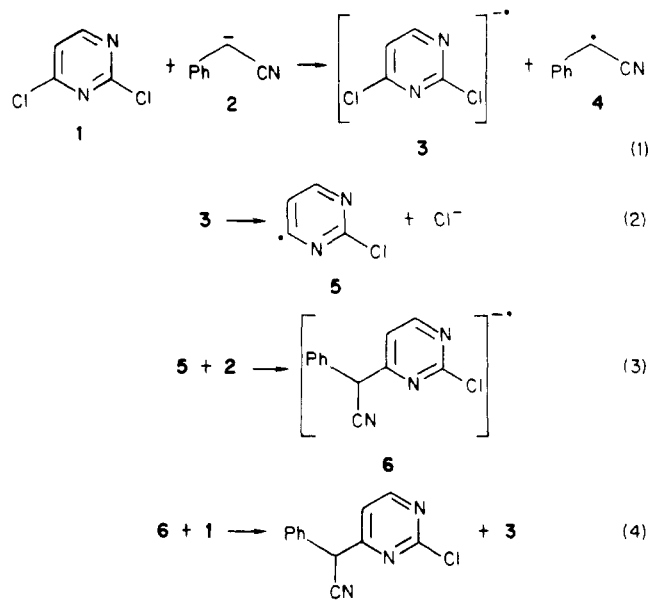
Recent studies of heteroaromatic $S_{RN}1$ reactions in our laboratories[2,3] have demonstrated that certain dihalogenated π-deficient nitrogen heterocycles react with ketone enolates and other carbanionic nucleophiles under photostimulation in liquid NH_3 to yield products resulting from displacement of one or both halogens depending upon the nature of the substrate and nucleophile. For example, photoinduced reaction of 2,4-dichloropyrimidine (**1**) with potassiophenylacetonitrile (**2**) gives exclusively monosubstitution product **7**, resulting from displacement of chlorine from C_4 via the $S_{RN}1$ mechanism shown in Scheme I.[3]

Results and Discussion

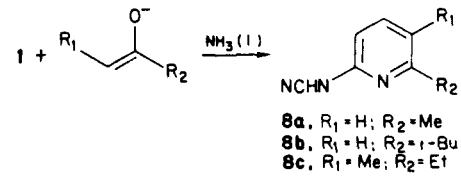
Since carbanion **2** and ketone potassium enolates have previously been observed to react in similar radical-chain fashion with mono- and dihalogenated nitrogen heterocycles,[3,4] we anticipated that photostimulated reactions of substrate **1** with ketone enolates would also lead to regioselective substitution at C_4. However, markedly different and unexpected results were obtained with the potassium enolates of acetone, pinacolone, and 3-pentanone.

Exposure of **1** to excess potassioacetone in liquid NH_3 under near-UV illumination afforded none of the expected mono- or disubstitution product. Instead, 2-(cyanamino)-6-methylpyridine (**8a**)[5] was isolated in 45% yield.

Scheme I



Similarly, (cyanamino)pyridines **8b** (68%) and **8c** (44%) were obtained from reactions of **1** with the potassium enolates of pinacolone and 3-pentanone, respectively.

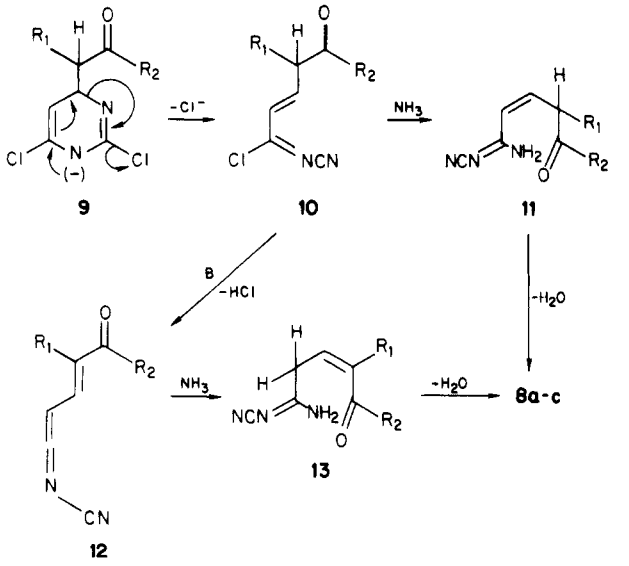


These pyrimidine–pyridine transformations were not inhibited by di-*tert*-butyl nitroxide (DTBN)[6] and pro-

(1) (a) Supported by NSF Grants No. CHE 77-13317 and CHE 80-22538, and NIH Grant No. NS 10197. (b) Abstracted in part from the Ph.D. dissertation of D. R. Carver, Virginia Polytechnic Institute and State University, August, 1979.
(2) Komin, A. P.; Wolfe, J. F. *J. Org. Chem.* **1977**, *42*, 2481.
(3) Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1983**, *48*, 1180.
(4) Moon, M. P.; Komin, A. P.; Wolfe, J. F.; Morris, G. F. *J. Org. Chem.* **1983**, *48*, 2392 and reference cited therein.
(5) Charonnat, R.; Le Perdriel, F. *Ann. Pharm. Fr.* **1968**, *26*, 469.

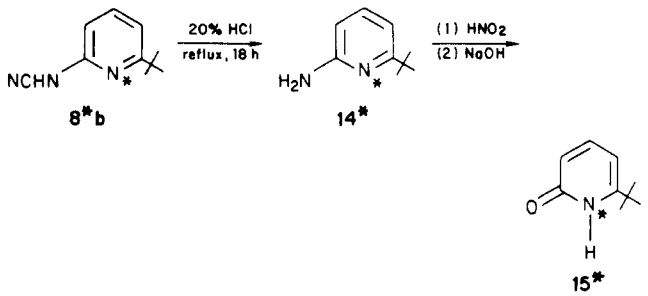
0022-3263/85/1950-3442$01.50/0

Scheme II



ceeded just as satisfactorily in the dark as with photostimulation. Thus they do not appear to be radical-chain processes. Rather, these reactions represent a new variation of the S_N(ANRORC)[7] mechanism as proposed in Scheme II. This series of reactions is initiated by addition of the ketone enolate to C_6 of the pyrimidine ring[8] to form an anionic dihydro intermediate **9**, which suffers ring cleavage and loss of chloride ion to give *N*-cyanoimino chloride **10**. Proceeding from intermediate **10**, two divergent pathways may be envisioned for the formation of the observed products. Ammonolysis of **10** could occur to yield *N*-cyanoamidine **11**.[9] Alternatively, **10** may experience enolate-induced elimination of hydrogen chloride, affording *N*-cyanoketenimine **12**, which then reacts with NH_3[10] to produce *N*-cyanoamidine **13**, a tautomer of **11**. Intramolecular cyclodehydration of either **11** or **13** followed by tautomerization yields (cyanamino)pyridines **8a–c**.

In order to test the credibility of the proposed mechanism, **8*b** was synthesized from **1** and pinacolone enolate



in ^{15}N-enriched NH_3[11] and subsequently degraded to 6-(*tert*-butyl)-2(1*H*)-pyridone (**15***). In agreement with Scheme I, mass spectrometric measurement of the intensities of the M and M + 1 peaks of **8*b** and **15*** indicated ^{15}N incorporation commensurate with that in the ^{15}N-labeled NH_3.

A few pyrimidine–pyridine ring transformations with carbanionic nucleophiles have been reported,[8a,12] but none of these involve reactions of halopyrimidines. Moreover, in all cases the conversion resulted in either displacement of the N_1–C_2–N_3 portion of the pyrimidine ring by a C–C–N fragment of the nucleophile or the pyrimidine N_1–C_2 was replaced by a C–C moiety from the nucleophile. In the present transformations, the C–C–N fragment which replaces N_1–C_2–N_3 arises from two sources rather than from a single nucleophilic reactant. Thus, the ketone enolate contributes the C–C fragment while NH_3 is the N donor.

The tendency for ketone enolates to react with **1** via the S_N(ANRORC) mechanism, while carbanion **2** participates in radical-chain substitution, may be attributed to several factors. For example, the two electron-withdrawing halogens and the unsubstituted 6-position of **1** invite nucleophilic addition, which is more favorable with the harder enolates than with the softer, more delocalized **2**. Conversely, initiation of the $S_{RN}1$ process (step 1, Scheme I) may be more facile with **2** than with the ketone enolates owing to lower (less positive) oxidation potential of the former relative to the later.[13]

The experimental simplicity and ready availability of starting materials make the present reactions, as well as those involving other enolate nucleophiles, potentially attractive for the synthesis of substituted pyridines and 2(1*H*)-pyridones.

Experimental Section

General Methods. All reactions were conducted under a nitrogen atmosphere. Photostimulated reactions were performed on a Rayonet RPR-240 reactor equipped with four 12.5-W bulbs with maximum emission at 350 nm. Quenching and processing of reactions were performed under atmospheric conditions.

Gas chromatographic (GC) analyses were carried out on a Varian 90-P instrument with columns of 2% Carbowax on chromasorb supports. Temperatures of 153–235 °C were used; benzoate and phthalate estes were employed as internal standards. Infrared (IR) spectra were recorded on a Perkin-Elmer 621 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-390 instrument, using tetramethylsilane as the internal standard. Melting points were taken on a Thomas-Hoover oil bath apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or Atlantic Microlab, Atlanta, GA.

Mass spectra and ^{15}N assays were determined on a Varian MAT-112 mass spectrometer. The extent of ^{15}N incorporation was determined as follows: each case was treated as a two-component mixture, and the composition which produced the best match between calculated and experimental spectra was found. The optimization procedure involved minimizing the sum of squares of errors between calculated and experimental intensities

(6) (a) Hoffman, A. K.; Feldman, A. M.; Geblum, E.; Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639. (b) Nelson, S. F.; Bartlett, P. D. *Ibid.* **1966**, *88*, 143.

(7) (a) de Valk, J.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1414. (b) van der Plas, H. C. *Acc. Chem. Res.* **1978**, 462.

(8) The electrophilicity of the C_6 position of pyrimidine has been well documented. For recent examples of ketone enolate addition to C_6, see: (a) Barczynski, P.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 256. (b) Oostveen, E. A.; van der Plas, H. C. *Recl. Trav. Chim Pays-Bas* **1979**, *98*, 441. (c) Carver, D. R.; Komin, A. P.; Hubbard, J. S.; Wolfe, J. F. *J. Org. Chem.* **1981**, *46*, 294.

(9) The probability of ammonolysis occurring before ring scission is remote in light of the unreactivity of **1** with liquid NH_3.

(10) For a review of the reactions of ketenimines with nitrogenous bases, see: Krow, G. R. *Angew. Chem.* **1971**, *10*, 435.

(11) Prepared by treating a solution of KNH_2 in liquid NH_3 with $(^{15}NH_4)_2SO_4$ followed by distillation. The ^{15}N-enriched ammonia was calculated to contain ca. 14% ^{15}N.

(12) (a) Albert, A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1794. (b) Oostveen, E. A.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 233. (c) Barczynski, P.; van der Plas, H. C. *J. Org. Chem.* **1982**, *47*, 1077. (d) Charushin, V. N.; van der Plas, H. C. *J. Org. Chem.* **1983**, *48*, 2667. (e) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4423. (f) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. *J. Org. Chem.* **1981**, *46*, 846. (g) Su, T.-L.; Watanabe, K. A. *J. Heterocycl. Chem.* **1982**, *19*, 1261.

(13) The oxidation potential ($E_{1/2}$) of dimethyl sodiomalonate, sodiacetylacetone, and methyl sodiocyanoacetate in 50% MeOH, 50% C_6H_6 with $LiClO_4$ or $NaClO_4$ at a graphite working electrode have been reported to be +0.87, +0.83, and +0.65 V, respectively. See; Schafter, H. *Chem.-Ing.-Tech.* **1969**, *41*, 179.

for (1) all peaks in the vicinity of the molecular ion, (2) all peaks in the vicinity of M-15, and (3) a combination of (1) and (2). All three methods gave good agreement; experimental error is ±1%.

Commercial anhydrous liquid NH_3 (Matheson) was used directly from the tank. Anhydrous ether was stored over molecular sieves (5A) for 24 h before use. Ketones were freshly distilled and stored over molecular sieves. Short-column chromatography using hexane–ethyl acetate mixtures was used for large-scale separations; silica gel with mesh size >230 was used. Chromatographic solvents were distilled prior to use.

Typical Reaction Procedures. One of the following procedures was used in reactions of ketone enolates with 2,4-dichloropyrimidine (1).

Procedure A: Potassium amide (11.25 mmol in 150–175 mL of liquid NH_3) was generated in a cylindrical Dewar flask (unsilvered) according to Hauser's procedure.[14] An anhydrous ethereal solution solution of the ketone (11.25 mmol) was added slowly (1.5 min) via syringe. After 5 min, the lamps were turned on. Substrate 1 (3.0 mmol) was then added as an ethereal solution. After an irradiation period of 15 min, the reaction mixture was poured into a 1-L beaker containing 3.5–4 g of solid NH_4Cl. The reaction vessel was washed with ether (2 × 100 mL) and the ethereal washings were added to the ammonia solution. The ammonia was allowed to evaporate; the evaporation was sometimes accelerated by warming the beaker on a hot plate. The ether was decanted and the ammonium salts were washed with ether (2 × 100 mL). The combined ethereal solutions were dried ($MgSO_4$) and filtered; the solvents were removed under reduced pressure to afford crude products.

Procedure B: Potassium amide (11.5 mmol in 200 mL of liquid NH_3) was generated in a 250-mL, three-necked flask equipped with a nitrogen inlet and a dry ice condenser. The ketone was added as an ethereal solution via syringe. The flask was wrapped with several layers of dark cloth and the room lights were extinguished. An ethereal solution of 1 was added via syringe. After a reaction period of 15 min, the reaction was quenched and worked up as described in procedure A. Inhibited reactions were conducted by adding 10 mol % of di-*tert*-butyl nitroxide (DTBN) based on substrate to the enolate solutions before addition of 1.

Reaction of 1 with Acetone Enolate. Procedure A and B gave a red tar after removal of the NH_3. Ether (100 mL) was added to the residue, followed by 5 mL of water and then enough 3 N HCl to bring the pH to 3.0. The layers were separated and the aqueous layer was further extracted with $CHCl_3$ (3 × 60 mL) and ethyl acetate (3 × 60 mL). The combined organic extracts were dried and filtered; the solvents were removed on a rotary evaporator to give a red solid. This material was chromatographed on 50 g of silica gel by using hexane and hexane–ethyl acetate (increasing amounts of ethyl acetate) to give 2-(cyanamino)-6-methylpyridine (**8a**), mp 213 °C, in 43% yield. The product was very insoluble even in polar solvents, and heating for recrystallization caused decomposition: IR (KBr) 1180, 1390, 1635, 2175 (CN), 2800, 3425 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 2.30 (s, 3 H, CH_3), 6.45 (d, 7.5 Hz, 1 H, PyH-3), 6.80 (d, 8 Hz, 1 H, PyH-5), 7.61 (t, 7.5, Hz, 1 H, PyH-4); MS, *m/e* (relative intensity) 133 (100), 106 (19), 92 (60); high-resolution MS calcd for $C_7H_7N_3$ 133.06398, found 133.0617. Anal. Calcd for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 62.31; H, 5.09; N, 31.14. Compound **8a** was identical with (^1H NMR, mmp) an authentic sample prepared from 2-amino-6-picoline according to the procedure of Charonnat and LePerdriel.[5]

(14) Hauser, C. R.; Harris, T. M. *J. Am. Chem. Soc.* **1958**, *80*, 63.

Reaction of 1 with Pinacolone Enolate. Procedure A or B gave identical results. Either procedure gave a yellow solid which was transformed into a white solid upon crystallization from $CHCl_3$–CCl_4. The product was identified as 2-(cyanamino)-6-(*tert*-butyl)pyridine (**8b**), mp 162–163 °C (68%): IR (neat) 1260, 1395, 1535, 1630, 2150 (CN), 2170 (CN), 3090, 3300 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, *t*-Bu), 6.63 (d, 7 Hz, 1 H, PyH-3), 7.50 (d, 8 Hz, 1 H, PyH-5), 7.71 (t, 7 Hz, 1 H, PyH-4); MS, *m/e* (relative intensity) 175 (46), 160 (100), 133 (39), 120 (22). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found (unlabeled compound): C, 68.34; H, 7.26; N, 24.24. ^{15}N-labeled **8*b**, which was similarly prepared in liquid NH_3 containing ca. 14% $^{15}NH_3$, showed 13.7% incorporation of ^{15}N by mass spectrometric analysis.

Reaction of 1 with 3-Pentanone Enolate. Procedure A and B gave the same results; the yield improved with a 30-min reaction period. Either procedure gave a yellow solid. Chromatography on 50 g of silica gel gave 2-(cyanamino)-5-methyl-6-ethylpyridine (**8c**) in 44% yield, mp 168–170 °C after recrystallization from EtOH–H_2O: IR (KBr) 1300, 1440, 1640, 2170 (CN), 2800, 3430 cm^{-1} (NH); ^1H NMR (acetone-d_6, Me_2SO-d_6) δ 1.17 (t, 7 Hz, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.66 (q, 7 Hz, 2 H, CH_2), 6.81 (d, 8 Hz, 1 H, PyH-3), 7.57 (d, 8 Hz, 1 H, PyH-4); MS, *m/e* (relative intensity) 161 (45), 160 (50), 92 (100). Anal. Calcd for $C_8H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 66.86; H, 6.95; N, 26.38.

Preparation of 2-Amino-6-(*tert*-butyl)pyridine (14) from 8b. A solution of **8b** (1.00 g, 5.7 mmol) in 50 mL of 20% hydrochloric acid was heated under reflux for 18 h, cooled, and added dropwise to a slurry of 50 g of powdered anhydrous Na_2CO_3 in 50 mL of ether. The ethereal solution was decanted from the solid residue, which was extracted with an additional 50 mL of ether. The combined ethereal solutions were dried over a 1:1 $MgSO_4$–Na_2CO_3 mixture and concentrated to a yellow liquid, which solidified on standing to give 0.83 g (97%) of **14**, mp 38–39 °C: ^1H NMR ($CDCl_3$) δ 1.24 (s, 9 H, *t*-Bu), 4.21 (br s, 2 H, NH_2), 6.20 (d, 7.5 Hz, 1 H, PyH-3), 6.58 (d, 7.5 Hz, 1 H, PyH-5), 7.24 (t, 7.5 Hz, 1 H, PyH-4); MS, *m/e* (relative intensity) 150 (44), 149 (34), 135 (100). Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found (unlabeled compound): C, 72.03; H, 9.43; N, 18.61.

Preparation of 6-(*tert*-Butyl)-2(1*H*)-pyridone (15) from 14. A solution of $NaNO_2$ (0.20 g, 2.9 mmol) in 2.0 mL of water cooled to 5 °C was added dropwise to a solution of **14** (0.37 g, 2.5 mmol) in 16 mL of 5% H_2SO_4 (0.80 g, 8.2 mmol) at 0 °C. After the addition was complete, the solution was stirred at 5 °C for 0.5 h and then a 25% NaOH solution was added dropwise until a pH of 5.0 was reached. At this point, 0.15 g of **15** precipitated as a pale yellow solid, mp 151–153 °C. The aqueous solution was saturated with NaCl and extracted with CH_2Cl_2 (2 × 25 mL). Distillation of the CH_2Cl_2 afforded another 0.18 g of **15**, mp 151–153 °C; total yield 0.33 g (89%). One recrystallization from ether–hexane gave nearly colorless crystals of **15**, mp 153 °C: ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 6.06 (d, 6.5 Hz, 1 H, PyH-5), 6.37 (d, 8.5 Hz, 1 H, PyH-3), 7.31 (dd, 6.5, 8.5 Hz, 1 H, PyH-4); MS, *m/e* (relative intensity) 151 (43), 150 (23), 136 (100). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found (unlabeled compound): C, 71.38; H, 8.70; N, 9.20).

The same procedures were used to prepare **14*** and **15***. From a sample of **8*b** containing 11.2% ^{15}N, **14*** and **15*** were obtained having ^{15}N enrichments of 12.0% and 11.2%, respectively.

Registry No. 1, 3934-20-1; **8a**, 80840-19-3; **8b**, 97634-81-6; **8c**, 97634-82-7; **14**, 97634-83-8; **15**, 58498-57-0; acetone, 67-64-1; pinacolone, 75-97-8; 3-pentanone, 96-22-0; acetone potassium enolate, 25088-58-8; pinacolone potassium enolate, 55440-76-1; 3-pentanone potassium enolate, 93304-74-6.