Pyridone Annulation by 4 + 2 Coupling of Dienolates with Nitriles and Nitrile Equivalents. A Solution to the Acetonitrile Problem

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Introduction

Assembly of 2-pyridones can be accomplished in a variety of ways, with many approaches described in Tieckelmann's extensive 1974 review.[2] New variations have been reported since, and additional reviews have appeared.[3] During the course of our investigations of 2-pyridone photochemistry,[4] we had the opportunity to explore the formation of a 2-pyridone by coupling a nitrile with a dienolate, retrosynthetically depicted in Figure 1. Several examples of this reaction are known. Condensation of nitriles with benzyl anions derived from *o*-methyl benzamides to form isoquinolinones has been described by a number of laboratories.[5] Condensation of nitriles with β-keto ester dianions (**3b**, $R^4 = O^-$) leads to 4-hydroxy-2-pyridones.[6] More recently, the dienolate dianions **3a**, prepared from unsaturated carboxylic acids, have been coupled with nitriles to yield pyridones.[7] These nitrile condensations often give high yields of pyridones when the nitrile substituent R^6 is aromatic or another nonenolizable group. When the nitrile is aliphatic, however, the yields suffer, and for acetonitrile (R^6 = methyl) some reactions are reported to fail.[5a,7] The reasonable speculation has been that deprotonation of the aliphatic nitriles by the nucleophile, followed by self-condensation,[8]

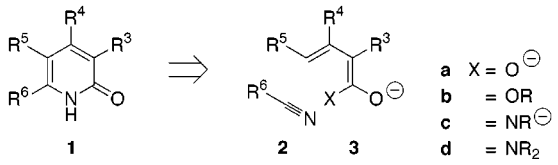

Figure 1. A nitrile−dienolate condensation approach to pyridone construction. The dienolate can take several forms.

is the culprit. The acid dianion methodology[7] is one of the more effective methods, but yields with acetonitrile are low (vide infra).

We required a 6-methyl-2-pyridone, with four ring carbons derived from a butenoic acid and one from acetonitrile, or their equivalents. During the course of this investigation we have surveyed the known approaches and report here an alternative two-step solution that provides reasonable overall yields.

As outlined in Figure 1, the dienolate component **3** can be derived from an acid, an ester, or an amide. For "simple" ester dienolates **3b**, condensation with nitriles would be expected to be unfavorable, based on pK_a values alone.[9−11] In the cases of the dienolates prepared from acids **3a**, and primary and secondary amides **3c**, the reactive species would be a dianion, with presumably enhanced nucleophilicity. A potential complication of this reaction is the well-known selectivity of dienolates for α-alkylation.[12] The selectivity with acylating reagents, however, with their potential for reversibility, has not been fully addressed.[13]

Results and Discussion

We began with 2-methylcyclopentenoic acid[14] **4** and its condensation with benzonitrile and acetonitrile, Scheme 1, following the method of Brun.[7] In each instance the desired pyridone was formed in yields comparable to those reported. Benzonitrile gave the pyridone **5a** in good yield. Unfortunately, simple changes in reaction conditions failed to improve the miserable yields of **5b** from acetonitrile. Reasoning that an amide-derived dienolate would be sufficiently nucleophilic, we also tried nitrile condensations with *N*,*N*-dimethyl amide **6**. This proved to be significantly better than with **4**, and with chiral substrate **7**[15] the yield from acetonitrile was 44%. Nevertheless, much room for improvement remained.

Attempts to capitalize on the moderate success with **6** and **7**, using the dianion of *N*-methyl amide **9** or the diisopropylamide **10**, failed completely. A similar disappointment met our attempts to employ a zinc dienolate

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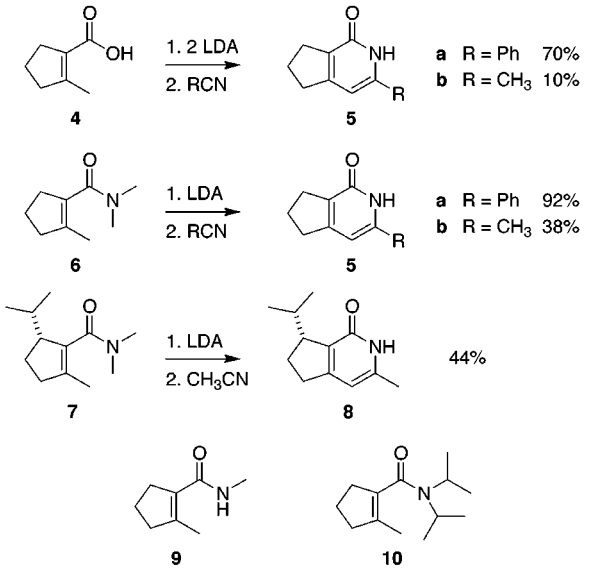
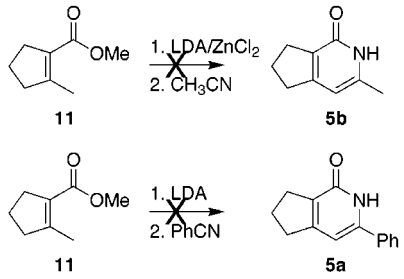
Scheme 1. Annulation of Acid and Amide Dienolates with Nitriles



Scheme 2. Unsuccessful Condensation Attempts



in a vinylogous Blaise reaction[16] with acetonitrile (Scheme 2). The simple expedient of condensing ester **11** with benzonitrile also failed, as expected.

On the other hand, ester enolates (but not dienolates[17,18]) have been successfully condensed with Weinreb amides.[19] The resulting δ-keto acrylates would be readily convertible to pyridones. Reaction of the dienolate derived from **11** with *N*-methoxy-*N*-methyl acetamide **12a** and butyramide **12b** both gave modest yields of the δ-keto esters **13b** and **13c**. Unreacted **11** was also isolated, consistent with the report that conversion of ester enolates with Weinreb amides are often difficult to drive to completion.[19] On the basis of unrecovered starting **11**, the yields of **13** are quite reasonable. Heating **13b** and **13c** with ethanolic ammonia led to a high yield of pyridones **5b** and **5c**. The chiral ester **14** also condensed well with the Weinreb acetamide **12b** and was readily converted to pyridone **8** in high yield. Condensation of the Weinreb acetamide **12b** with *N*,*N*-dimethyl amide **7** proceeded in good yield, but attempts to convert the keto-tertiary amide product to a pyridone with ammonia was unsuccessful.

Conclusions

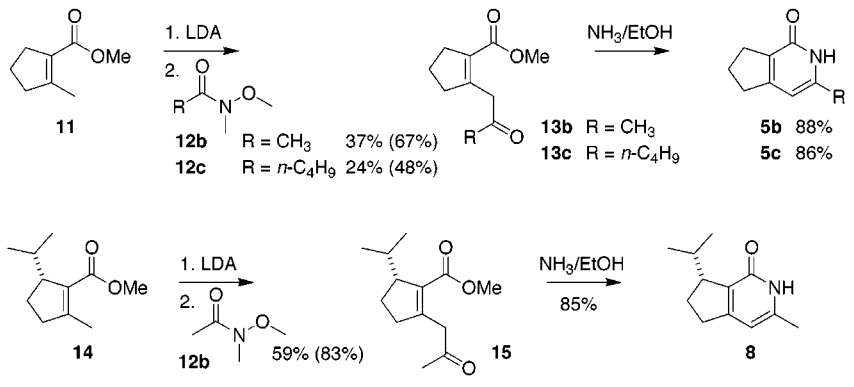
The condensation of Weinreb amides with dienolates is a useful and practical approach to pyridone annulation, particularly for enolizable substrates. On the basis of the work of Turner, it is likely that an excess of dienolate would enhance the condensation yields.[19] For all the reactions described here, a small excess of the electrophile was employed. Condensations of *N*,*N*-dimethyl amide derived dienolates with nitriles should prove useful as well.

Experimental Section

3-Phenyl-2,5,6,7-tetrahydro-[2]pyrindin-1-one (5a). To a −78 °C solution of **6** (107 mg, 0.70 mmol) in THF (8 mL) was added dropwise a solution of LDA (5 mL of a 0.25 M solution in THF, 1.25 mmol) and the mixture stirred for 1 h. A solution of benzonitrile (0.097 mL, 0.957 mmol) in THF (3 mL) was added dropwise, and the mixture was allowed to warm to room temperature and stirred for 24 h. After dilution with 10% HCl and extraction with ethyl acetate, the combined organics were dried and concentrated to give **5a** (135.8 mg, 92%) as a light yellow solid. Recrystallization from methanol/ethyl acetate gave colorless needles. R_f = 0.21 (silica gel, 1:19 methanol/methylene chloride). mp = 214−5 °C (lit. 210−1 °C[20]). ^{1}H NMR ($CDCl_3$) δ 11.15 (s, 1H), 7.70 (m, 2H), 7.48 (m, 3H), 6.48 (s, 1H), 2.89 (m, 4H), 2.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 162.5, 157.2, 144.9, 133.9, 130.7, 129.6, 129.0, 128.5, 127.3, 126.4, 103.2, 34.4, 29.4, 23.5. IR (neat): 1633, 1609, 1597 cm^{-1}.

3-Methyl-2,5,6,7-tetrahydro-[2]pyrindin-1-one (5b from 6). Following the procedure used for **5a**, using **6** (135.4 mg, 0.885 mmol) and acetonitrile (0.15 mL, 2.9 mmol) gave **5b** (0.05 g, 38%) as a colorless solid. Recrystallization from ethyl acetate gave colorless needles. R_f = 0.45 (silica gel, 1:19 methanol/methylene chloride), mp = 158−9 °C (lit. 160−1 °C[20]). ^{1}H NMR ($CDCl_3$) δ 12.24 (s, 1H), 6.02 (s, 1H), 2.79 (t, 4H), 2.32 (s, 3H), 2.04 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 163.3, 157.8, 143.5, 128.2, 104.2, 34.2, 29.2, 23.5, 18.9. IR (neat): 1648, 1566, 1466 cm^{-1}. MS (EI+)

Scheme 3. Condensation of Dienolates with Enolizable Weinreb Amides[a]



[a] Conversion-based yields are in parentheses.

m/*z* (%): 149 (M^+, 71), 148 (100), 134 (9), 120 (8). Exact mass (M − H) *m*/*z*: calculated 148.0762, found: 148.0768.

3-Methyl-2,5,6,7-tetrahydro-[2]pyrindin-1-one (5b from 11). To a −78 °C solution of **11** (420 mg, 3.0 mmol) in THF (3 mL) was added dropwise to a −78 °C solution of LDA (4.5 mmol in 20 mL of THF). After 1.5 h, a solution of *N*-methoxy-*N*-methyl acetamide (460 mg, 4.5 mmol) was added and stirring continued at −78 °C for 2 h. A 10% HCl solution (5 mL) was added, the mixture was warmed to room temperature and then diluted with sat. NH_4Cl. The aqueous phase was extracted with ethyl acetate, the combined organics were dried over $MgSO_4$ and purified by flash chromatography, initially with 1:19 ethyl acetate/hexanes, to give recovered **11** (232 mg, 55%) and then with 3:17 ethyl acetate/hexanes, to give methyl 2-(2-oxo-propyl)-1-cyclopentenecarboxylate **13b** (202 mg, 37%; 67% based on recovered **11**). R_f = 0.35 (silica gel, 1:4 ethyl acetate/hexanes), ^{1}H NMR ($CDCl_3$): δ 3.769 (s, 2H), 3.710 (s, 3H), 2.662 (t, J = 7.5 Hz, 2H), 2.515 (t, J = 7.8 Hz, 2H), 2.193 (s, 3H), 1.873 (m, 2H). ^{13}C NMR ($CDCl_3$): 204.9, 166.0, 151.8, 130.1, 51.0, 44.9, 39.0, 33.2, 29.9, 21.3. IR (neat): 2952, 1713, 1644, 1434, 1358, 1298, 1265 cm^{-1}. MS (EI) *m*/*z* (%): 182 (M^+, 5), 150 (100), 108 (42), 81 (70), 43 (64). Exact mass *m*/*z*: calculated 182.0943, found 182.0944.

Keto ester **13b** (80 mg, 0.44 mmol) was dissolved in absolute ethanol (5 mL) in a resealable tube. The solution was saturated with ammonia, sealed, and heated to 130 °C for 4 h. Removal of the solvent gave **5b** (58 mg, 88%).

3-Butyl-2,5,6,7-tetrahydro-[2]pyrindin-1-one (5c from 11). Following the procedure described for **5b**, **11** (420 mg, 3.0 mmol) and *N*-methoxy-*N*-methyl *n*-pentamide (770 mg, 4.5 mmol) led to recovered **11** (216 mg) and methyl 2-(2-oxo-hexyl)-1-cyclopentenecarboxylate **13c** (159 mg, 24%; 48% based on recovered **11**). R_f = 0.52 (silica gel, 1:4 ethyl acetate/hexanes), ^{1}H NMR ($CDCl_3$): δ 3.756 (s, 2H), 3.701 (s, 3H), 2.652 (t, J = 8.4 Hz, 2H), 2.496 (m, 4H), 1.860 (m, 2H), 1.557 (m, 2H), 1.318 (m, 2H), 0.894 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 107.4, 166.1, 152.1, 130.0, 51.0, 4.1, 42.5, 39.0, 33.2, 25.8, 22.2, 21.4, 13.8. IR (neat): 2955, 2936, 2871, 1712, 1643, 1434, 1359 cm-1. MS (EI) *m*/*z* (%): 224 (M^+, 3), 192 (40), 140 (21), 108 (23), 85 (84), 57 (100). Exact mass *m*/*z*: calculated 224.1412, found 224.1412.

Treatment of **13c** (57 mg, 0.25 mmol) with ethanolic ammonia as described for **13b**, heating at 130 °C for 6 h, led to isolation of **5c** (42 mg, 86%). R_f = 0.35 (silica gel, 1:4 methanol/methylene chloride), ^{1}H NMR ($CDCl_3$): δ 11.9 (b, 1H), 6.011 (s, 1H), 2.788 (t, J = 7.5 Hz, 3H), 2.548 (t, J = 7.5 Hz, 2 H), 2.036 (m, 2H), 1.625 (m, 2H), 1.364 (m, 2H), 0.917 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 163.1, 157.5, 147.9, 128.5, 103.2, 34.3, 32.7, 30.8, 29.2, 23.5, 22.1, 13.7. IR (NaCl Plate): 2963, 2871, 1632, 1464 cm^{-1}. MS (EI) *m*/*z* (%): 191 (M^+, 31), 162 (10), 149 (100). Exact mass *m*/*z*: calculated 191.1310, found 191.1308.

***N,N*-Dimethyl 5-(*R*)-Isopropyl-2-methyl-1-cyclopentenecarboxamide (7).** To a solution of 5-(*R*)-isopropyl-2-methyl-1-cyclopentenecarboxylic acid[15] (4.35 g, 25 mmol) in benzene (50 mL) was slowly added thionyl chloride (10.9 mL) in benzene (15 mL). The solution was heated to reflux for 4 h, evaporated, and redissolved in benzene (50 mL). The solution was cooled in an ice bath and dimethylamine (11 mL in 20 mL benzene) was added dropwise. After stirring for 1 h the mixture was diluted with water and extracted with ethyl acetate. The combined organics were washed with water, dried over Na_2SO_4, and concentrated in vacuo to give a dark oil which was purified by flash chromatography (1:19 methanol/methylene chloride) to give unsaturated amide **7** (4.3 g, 96%). R_f = 0.47 (silica gel, 1:19 methanol/methylene chloride). ^{1}H NMR ($CDCl_3$) δ 2.99 (s, 7H), 2.27 (m, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 1.66 (s, 3H), 1.58 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 140.0, 134.6, 54.4, 37.6. 37.3, 34.1, 30.3, 24.2, 20.9, 17.9, 15.3. IR (neat): 1621, 1445, 1391, 1367 cm^{-1}.

***N,N*-Dimethyl 2-Methyl-1-cyclopentenecarboxamide (8 from 7).** Following the procedure used for **5a**, using **7** (171 mg, 0.88 mmol) and acetonitrile (0.46 mL, 8.8 mmol), gave **8** (73 mg, 44%) as a faintly yellow solid. R_f = 0.24 (silica gel, 1:19 methanol/methylene chloride). mp = 100−102 °C. $[\alpha]_D$ = 28° ($CHCl_3$, 0.08). ^{1}H NMR ($CDCl_3$) δ 11.58 (s, 1H), 5.97 (s, 1H), 3.25 (t, 1H), 2.70 (m, 2H), 2.52 (m, 1H), 2.271 (s, 3H), 1.94 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 157.9, 143.3, 130.3, 103.9, 48.9, 33.4, 28.7, 23.9, 21.3, 18.9, 16.8. IR (neat) 1638, 1564, 1465, 1433 cm^{-1}. MS (EI) *m*/*z* (%): 191 (M^+, 17), 149 (16), 148 (100). Exact mass *m*/*z*: calculated 191.1310, found 191.1303.

Methyl 5-(*R*)-Isopropyl-2-(2-oxo-propyl)-1-cyclopentenecarboxyate (15). To a −78 °C solution of **14** (182.3 mg, 1.00 mmol) in THF (10 mL) was added dropwise a solution of LDA (0.60 mL of a 2.0 M solution in THF, 1.2 mmol). After 1.5 h, a solution of *N*-methoxy-*N*-methyl acetamide (130 mg, 1.26 mmol) was added and stirring continued at −78 °C for 2 h. A 10% HCl solution (1 mL) was added, and the mixture was warmed to room temperature and then diluted with sat. NH_4Cl. The aqueous phase was extracted with ethyl acetate, and the combined organics were dried over $MgSO_4$ and purified by Flash chromatography, initially with 1:19 ethyl acetate/hexanes, to give recovered **14** (54 mg, 30%) and then with 1:4 ethyl acetate/hexanes, to give **15** (133 mg, 59%). R_f = 0.39 (silica gel, 1:4 ethyl acetate/hexanes), $[\alpha]_D$ = −36.7° (Et_2O, 0.105), ^{1}H NMR ($CDCl_3$): δ 3.78 (d, J = 15.6, 1H), 3.71 (s, 3H), 3.61 (d, J = 15.6, 1H), 3.01−3.08 (m, 1H), 2.30−2.60 (m, 2H), 2.19 (s, 3H), 2.02−2.15 (m, 1H), 1.87 (m, 1H), 1.71 (m, 1H), 0.910 (d, J = 6.9 Hz), 0.735 (d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 204.8, 166.2, 151.2, 133.3, 51.6, 50.8, 45.1, 38.2, 29.8, 29.7, 22.3, 21.1, 16.4. IR (neat): 2956, 1712, 162, 143, 1357, 1298, 1277, 1254 cm^{-1}. MS (EI) *m*/*z* (%): 224 (M^+, 2), 192 (59), 149 (100), 107 (34), 43 (29). Exact mass *m*/*z*: calculated 224.1412, found: 224.1423.

Methyl 5-(*R*)-Isopropyl-2-methyl-1-cyclopentenecarboxylate (8 from 15). Keto ester **15** (133 mg, 0.59 mmol) was dissolved in absolute ethanol (5 mL) in a resealable tube. The solution was saturated with ammonia, sealed, and heated to 130 °C for 4 h. Removal of the solvent gave **8** (45.2 mg, 85%) which was pure by NMR.

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Supporting Information Available: Proton NMR spectra for **5a**−**c**, **7**, **8**, **13b**, **13c**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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