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Nucleophilic alkenoylation of aldehydes with metalated α-aminonitriles: regioselective synthesis of α-hydroxyenones

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Abstract

An efficient regioselective two-step synthesis of α-hydroxyenones **3a–p** is reported. The methodology involves nucleophilic addition of metalated β,γ-unsaturated-α-aminonitriles to aldehydes, followed by a mild silver nitrate induced hydrolysis of the aminonitrile adducts to afford the title compounds in overall yields of 61–83%. © 1999 Elsevier Science Ltd. All rights reserved.

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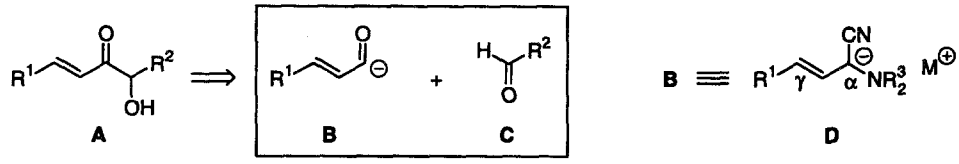
Multifunctional α-hydroxyenones **A** are potentially versatile building blocks for organic syntheses. Besides the fact that they include α-hydroxyketone moieties, which are structural subunits of many natural products,[1] it has been shown that the stereoselective reduction of the ketone function, followed by protection of the resulting diol and oxidative cleavage of the double bond, may provide interesting intermediates for amino-sugar synthesis.[2] In addition, hydroxyenones have been utilised as suitable precursors for the synthesis of cyclopentanones via Nazarov cyclisation.[3]

The retrosynthetic scheme outlined (Scheme 1) has previously been considered for the synthesis of β,γ-unsaturated-α-hydroxyketones **A**, requiring the addition of a synthetic equivalent of the α,β-unsaturated acyl anion **B** (Umpolung[4]) to aldehydes **C**. Towards this goal, a great deal of attention has been devoted to the development of both achiral and chiral synthetic equivalents of **B**, such as metalated heteroatom-stabilised allylic anions,[3,5,6] organometallic zirconium[7] or vinyl lithium reagents.[8]



Scheme 1.

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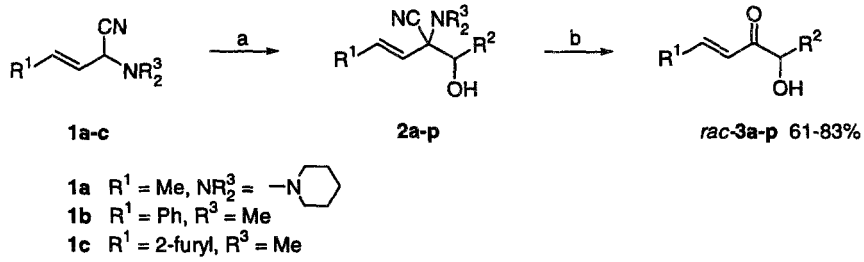
Amongst these studies, metalated β,γ-unsaturated-α-aminonitriles **D** are particularly interesting, owing to the advantage of the mild hydrolytic cleavage of aminonitriles to regenerate the carbonyl group. However, regioselectivity is always a crucial factor in the use of such ambient allylic anions, since reaction with an electrophile may occur either from the α- or the γ-site of the anion, providing an acyl anion or a homoenolate synthetic equivalent,[9,10] respectively. Jacobson et al.[3b] reported the addition of a lithiated crotonaldehyde derived aminonitrile **D** (R^1=R^3=Me) to ketones, and observed that addition occurred at the α-site under kinetically controlled conditions at low temperature, while the reaction took place at the γ-site at higher temperatures.

This paper reports the addition of metalated α-aminonitriles **D** to aldehydes as part of a convenient two-step procedure for the synthesis of α-hydroxyenones **A**.

The three different α-aminonitriles **1a–c** (Scheme 2) used for this study were previously prepared by Strecker synthesis from the parent α,β-unsaturated aldehydes.[3b,10a,11] Subsequent metalation was carried out by treatment of the aminonitriles **1a–c** with one equivalent of lithium diisopropylamide (LDA), in tetrahydrofuran at –78°C for 30–50 min. After the addition of a variety of aldehydes and subsequent stirring for 30 min–2 h at –78°C, the resulting mixtures were quenched with a saturated aqueous solution of ammonium chloride and subjected to standard work-up. The crude adducts **2a–p** could be characterised by ^{1}H NMR spectroscopy as a mixture of two diastereomers (ratios from 2:1 to 6:1). The additions were observed to have taken place regioselectively at the α-site of the metalated aminonitriles since no product resulting from addition of the aldehydes at the γ-position could be detected by ^{1}H NMR spectroscopy. One equivalent of aldehyde was sufficient for reaction with metalated **1a**, whereas a slight excess (1.5 equivalents) was necessary for completion of the addition in the case of the aminonitriles **1b** and **1c**.



Scheme 2. Reagents and conditions: (a) 1. LDA, THF, –78°C, 30–50 min; 2. R^2CHO, –78°C, 30 min–2 h; 3. sat. aqueous NH_4Cl; (b) $AgNO_3$, THF/H_2O, rt, 15–60 min

In the next step, the crude adducts **2a–p** underwent mild hydrolysis[12] induced by the addition of an aqueous silver nitrate solution (2 equivalents) to a THF solution of the adducts **2a–p**, resulting in the rapid formation of a dark grey silver cyanide precipitate. After stirring at room temperature for 15–60 min, the precipitate was removed by filtration through Celite. Standard aqueous work-up and purification by flash chromatography (SiO_2, ether/petroleum ether) provided the α-hydroxyenones **3a–p** in good overall yields (61–83%), which were fully characterised by ^{1}H and ^{13}C NMR, IR, MS and elemental analysis.

The results of this study are summarised in Table 1. In order to demonstrate the applicability of our methodology, aminonitriles derived from crotonaldehyde, (*E*)-cinnamaldehyde or 3-(*E*)-(2-furyl)-acrolein were investigated. These compounds were found to react with a wide range of aldehydes, bearing aliphatic, benzylic, or aromatic substituents, providing the α-hydroxyenones **3a–f**, **3g–k** and **3l–p**, respectively. However, nucleophilic addition of the metalated aminonitriles **1b** and **1c** to benzaldehyde was unsuccessful, affording a complex mixture of products.

Table 1
Synthesis of the α-hydroxyenones **3a–p**[13,14]

3a-f	R^1	R^2	yield[a] (%)	**3g-k**[b]	R^1	R^2	yield[a] (%)	**3l-p**[b]	R^1	R^2	yield[a] (%)
3a	Me	*n*-Bu	83	**3g**	Ph	*n*-Bu	78	**3l**	2-furyl	*n*-Bu	78
3b	Me	*i*-Pr	69	**3h**	Ph	*i*-Pr	77	**3m**	2-furyl	*i*-Pr	68
3c	Me	*c*-hex	62	**3i**	Ph	*c*-hex	67	**3n**	2-furyl	*c*-hex	62
3d	Me	Bn	61	**3j**	Ph	Bn	70	**3o**	2-furyl	Bn	72
3e	Me	CH_2CH_2Ph	70	**3k**	Ph	CH_2CH_2Ph	69	**3p**	2-furyl	CH_2CH_2Ph	72
3f	Me	Ph	68								

[a] Overall yield from **1a-c** after purification by chromatography. [b] 1.5 equivalents of aldehyde were necessary for completion of the addition reaction for **3g-k** and **3l-p**.

As regards the regioselectivity of the addition of the cinnamaldehyde derivative **1b**, it should be noted that earlier work by Fang et al.[10b] reported only γ-additions of a chiral equivalent of **1b** (*N*-methyl ephedrine as the amine moiety) to propionaldehyde, under similar reaction conditions. The opposite regioselectivity toward aliphatic aldehydes observed in the work reported here probably results from a less hindered α-position of the metalated aminonitrile.

In summary, this paper describes an efficient and regioselective synthesis of α-hydroxyenones via addition of metalated β,γ-unsaturated-α-aminonitriles to aldehydes. The methodology proceeds in two steps using only simple reactants and experimental conditions and shows that metalated β,γ-unsaturated-α-aminonitriles, when reacting with aldehydes, are suitable synthetic equivalents of α,β-unsaturated acyl anion synthons. An additional advantage of aminonitriles is the possibility to introduce chirality via the amino group, in order to carry out asymmetric nucleophilic acylations.[15] Further studies towards a stereoselective variant of this process are under current investigation in these laboratories.

Acknowledgements

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References

1. Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919–934.
2. Hiyama, T.; Kobayashi, K.; Fujita, M. *Tetrahedron Lett.* **1984**, *25*, 4959–4962.
3. (a) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395–405. (b) Jacobson, R. M.; Clader, J. W. *Tetrahedron Lett.* **1980**, *21*, 1205–1208.
4. Seebach, D. *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.
5. (a) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665–722 and references therein. (b) Zhang, G.; Jiang, J. *J. Org. Chem.* **1995**, *60*, 7589–7596. (c) Prandi, C.; Venturello, P. *J. Org. Chem.* **1994**, *59*, 5458–5462. (d) Prandi, C.; Venturello, P. *Tetrahedron* **1994**, *50*, 12463–12468. (e) Hünig, S.; Schäfer, M.; Schweeberg, W. *Chem. Ber.* **1993**, *126*, 205–210. (f) Takahashi, K.; Honma, A.; Ogura, K.; Iida, H. *Chem. Lett.* **1982**, 1263–1266.

6. (a) Reggelin, M.; Tebben, P.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 2915–2918. (b) Tebben, P.; Reggelin, M.; Hoppe, D. *Tetrahedron Lett.* **1989**, *30*, 2919–2922. (c) Fang, J. M.; Chou, W. C.; Lee, G. H.; Peng, S. M. *J. Org. Chem.* **1990**, *55*, 5515–5519. (d) Fang, J. M.; Chen, M. Y.; Yang, W. J. *Tetrahedron Lett.* **1988**, *29*, 5937–5938. (e) Kirsten, C. N.; Herm, M.; Schrader, T. H. *J. Org. Chem.* **1997**, *62*, 6882–6887.
7. (a) Harada, S.; Taguchi, T.; Tabuchi, N.; Narita, K.; Hanzawa, Y. *Angew. Chem.* **1998**, *110*, 1796–1797; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1696–1698. (b) Ito, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 5829–5830.
8. (a) Braun, M.; Hild, W. *Angew. Chem.* **1984**, *96*, 701–702; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 723–724. (b) Mahler, H.; Braun, M. *Chem. Ber.* **1991**, *124*, 1379–1395.
9. (a) Hoppe, D. *Angew. Chem.* **1984**, *96*, 930–946; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948 and references therein. (b) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365–390 and references therein.
10. For homoenolate additions with metalated β,γ-unsaturated-α-aminonitriles see: (a) Ahlbrecht, H.; Vonderheid, C. *Synthesis* **1975**, 512–515. (b) Chang, C. J.; Fang, J. M.; Liao, L. F. *J. Org. Chem.* **1993**, *58*, 1754–1761. (c) Fang, J. M.; Chang, C. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1787–1788. (d) Fang, J. M.; Chang, H. T.; Lin, C. C. *J. Chem. Soc., Chem. Commun.* **1988**, 1385–1386. (e) Lesur, B.; Toye, J.; Chantrenne, M.; Ghosez, L. *Tetrahedron Lett.* **1979**, *20*, 2835–2838.
11. Dyke, S. F.; Tiley, E. P.; White, A. W. C.; Gale, D. P. *Tetrahedron* **1975**, *31*, 1219–1222.
12. Chauffaille, J.; Hebert, E.; Welvart, Z. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1645–1648.
13. Typical experimental procedure: LDA was prepared by dropwise addition of *n*-BuLi (1.6 M solution in hexane, 1.16 ml, 1.86 mmol) to a THF (5 ml) solution of diisopropylamine (0.26 ml, 1.85 mmol) and stirring at 0°C for 30 min. The mixture was cooled to –78°C and a THF (5 ml) solution of the aminonitrile **1b** (309 mg, 1.66 mmol) was added dropwise via syringe to give a deep orange solution. After stirring for 35 min, valeraldehyde (213 mg, 2.47 mmol) was added (neat) and the mixture stirred for 1.5 h. The reaction was quenched at –78°C with saturated aqueous NH_4Cl solution (20 ml) and extracted with ether (3×20 ml). The combined extracts were washed with brine (20 ml), water (2×20 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo at room temperature. The resulting yellow oil was dissolved in THF (10 ml) and treated with an aqueous solution (1.5 ml) of $AgNO_3$ (0.5 g, 2.94 mmol), inducing rapid formation of a AgCN precipitate. After stirring at room temperature for 40 min, the solution was filtrated through a pad of Celite and the precipitate washed with ether (2×20 ml) and water (20 ml). The aqueous phase was extracted with ether (3×20 ml), the combined organic phase washed with brine (2×20 ml) and water (20 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. Purification by flash chromatography (SiO_2, Et_2O/petroleum ether 1:3) afforded the hydroxyenone **3g** (283 mg, overall yield 78%) as a pale yellow oil.
14. Selected spectroscopic data: **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (m, 3H, $(CH_2)_3CH_3$), 1.24–1.57 (m, 5H) and 1.73–1.89 (m, 1H, $(CH_2)_3CH_3$), 1.95 (dd, *J*=6.9, *J*=1.6, 3H, CH_3CH=CH), 3.60 (broad s, 1H, CHOH), 4.35 (broad m, 1H, CHOH), 6.27 (dq, *J*=15.4, *J*=1.6, 1H, CH=CHCO), 7.06 (dq, *J*=15.7, *J*=6.9, 1H, CH=CHCO); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.56, 18.24, 22.21, 26.57, 33.68, 74.71, 126.10, 144.89, 200.29; IR (neat): 3464 (OH), 1692 (C=O), 1632 (C=C) cm^{-1}; MS (70 eV, EI): *m/z* (%)=(M$^{\cdot+}$ not detected), 100 (8), 87 (15), 69 (100), 57 (6), 45 (8). Anal. calcd for $C_9H_{16}O_2$ (156.22): C, 69.19; H, 10.32; found C, 68.62; H, 10.21; **3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.94 (dd, *J*=6.9, *J*=1.6, 3H, CH_3CH=CH), 2.86 (dd, *J*=14.0, *J*=7.1, 1H) and 3.10 (dd, *J*=14.0, *J*=4.7, 1H, CH_2Ph), 3.55 (broad d, *J*=5.2, 1H, CHOH), 4.58 (m, 1H, CHOH), 6.28 (dq, *J*=15.7, *J*=1.6, 1H, CH=CHCO), 7.03 (dq, *J*=15.7, *J*=6.9, 1H, CH=CHCO), 7.19–7.31 (m, 5H, C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=18.35, 40.44, 75.45, 126.47, 126.55, 128.07, 129.13, 136.29, 145.37, 199.27; IR (neat): 3458 (OH), 1690 (C=O), 1630 (C=C) cm^{-1}; MS (70 eV, EI): *m/z* (%)=190 (M$^{\cdot+}$, 1), 172 (100), 121 (77), 103 (68), 91 (99), 69 (69), 65 (17). Anal. calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42; found: C, 75.36; H, 7.43; **3g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (m, 3H, $(CH_2)_3CH_3$), 1.26–1.67 (m, 5H) and 1.84–1.95 (m, 1H, $(CH_2)_3CH_3$), 3.70 (broad d, *J*=5.2, 1H, CHOH), 4.47 (m, 1H, CHOH), 6.86 (d, *J*=15.9, 1H, CH=CHCO), 7.39–7.43 (m, 3H) and 7.57–7.60 (m, 2H, C_6H_5), 7.76 (d, *J*=16.2, 1H, CH=CHCO); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.63, 22.28, 26.65, 33.70, 75.42, 120.19, 128.29, 128.71, 130.74, 133.76, 144.26, 200.52; IR (neat): 3464 (OH), 1685 (C=O), 1610 (C=C) cm^{-1}; MS (70 eV, EI): *m/z* (%)=218 (M$^{\cdot+}$, 8), 131 (100), 103 (25), 77 (14), 69 (11), 57 (7). Anal. calcd for $C_{14}H_{18}O_2$ (218.29): C, 77.03; H, 8.31; found: C, 76.81; H, 8.29; **3j**: mp 72–74°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.98 (dd, *J*=14.0, *J*=6.6, 1H) and 3.14 (dd, *J*=14.0, *J*=5.2, 1H, CH_2Ph), 3.66 (d, *J*=5.5, 1H, CHOH), 4.69 (broad q, *J*=5, 1H, CHOH), 6.78 (d, *J*=15.9, 1H, CH=CHCO), 7.20–7.54 (m, 10H, $2C_6H_5$), 7.70 (d, *J*=15.9, 1H, CH=CHCO); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=40.59, 76.28, 120.65, 126.57, 128.20, 128.37, 128.74, 129.24, 130.83, 133.78, 136.28, 144.39, 199.53; IR (KBr): 3366 (OH), 1665 (C=O), 1594 (C=C) cm^{-1}; MS (70 eV, EI): *m/z* (%)=252 (M$^{\cdot+}$, 33), 133 (28), 105 (64), 91 (100), 65 (12). Anal. calcd for $C_{17}H_{16}O_2$ (252.31): C, 80.93; H, 6.39; found: C, 80.86; H, 6.43; **3l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (m, 3H, $(CH_2)_3CH_3$), 1.25–1.65 (m, 5H) and 1.81–1.96 (m, 1H, $(CH_2)_3CH_3$), 3.70 (broad s, 1H, CHOH), 4.41 (dd, *J*=7.1, *J*=3.6, 1H, CHOH), 6.52 (dd, *J*=3.3, *J*=1.6, 1H, furyl *H-4*), 6.74 (d, *J*=15.4, 1H, CH=CHCO), 6.74 (d, *J*=3.6,

1H, furyl *H-3*), 7.52 (d, *J*=15.7, 1H, *CH*=CHCO), 7.53 (broad s, 1H, furyl *H-5*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.60, 22.27, 26.62, 33.56, 75.54, 112.49, 116.86, 117.40, 129.94, 145.13, 150.57, 200.14; IR (neat): 3455 (OH), 1681 (C=O), 1607 (C=C) cm^{-1}; MS (70 eV, EI): *m/z* (%)=208 ($M^{\cdot+}$, 6), 121 (100), 94 (45), 69 (13), 65 (28). Anal. calcd for $C_{12}H_{16}O_3$ (208.25): C, 69.21; H, 7.74; found: C, 69.52; H, 7.75; **3o**: mp 64–66°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.92 (dd, *J*=14.0, *J*=6.9, 1H) and 3.16 (dd, *J*=14.3, *J*=4.7, 1H, CH_2Ph), 3.62 (d, *J*=5.7, 1H, CH*OH*), 4.63 (m, 1H, *CH*OH), 6.50 (dd, *J*=3.3, *J*=1.6, 1H, furyl *H-4*), 6.71 (d, *J*=3.3, 1H, furyl *H-3*), 6.76 (d, *J*=15.4, 1H, CH=*CH*CO), 7.17–7.31 (m, 5H, C_6H_5), 7.48 (d, *J*=15.7, 1H, *CH*=CHCO), 7.52 (d, *J*=1.6, 1H, furyl *H-5*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=40.23, 76.30, 112.58, 117.07, 117.71, 126.48, 128.09, 129.22, 130.14, 136.26, 145.28, 150.61, 199.08; IR (KBr): 3479 (OH), 1681 (C=O), 1607 (C=C) cm^{-1}; MS (70 eV, EI): *m/z* (%)=242 ($M^{\cdot+}$, 23), 224 (23), 151 (7), 121 (100), 94 (24), 91 (28), 81 (27), 65 (22). Anal. calcd for $C_{15}H_{14}O_3$ (242.27): C, 74.36; H, 5.82; found: C, 74.42; H, 5.97.

15. (a) Enders, D.; Lotter, H.; Maigrot, N.; Mazaleyrat, J. P.; Welvart, Z. *Nouv. J. Chim.* **1984**, *8*, 747–750. (b) Enders, D.; Kirchhoff, J.; Mannes, D.; Raabe, G. *Synthesis* **1995**, 659–666. (c) Enders, D.; Mannes, D.; Raabe, G. *Synlett* **1992**, 837–839. (d) Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem.* **1990**, *102*, 226–228; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 179–181. (e) Enders, D.; Kirchhoff, J.; Lausberg, V. *Liebigs Ann.* **1996**, 1361–1366. (f) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, 63–72.