Pergamon

Tetrahedron Letters 42 (2001) 381–383

TETRAHEDRON LETTERS

2-Acetoxyacrylonitrile: use as electrophile equivalent to acetaldehyde in the asymmetric Michael reaction using chiral imines

Laurent Keller, Cheikhou Camara, Antonio Pinheiro, Françoise Dumas* and Jean d'Angelo*

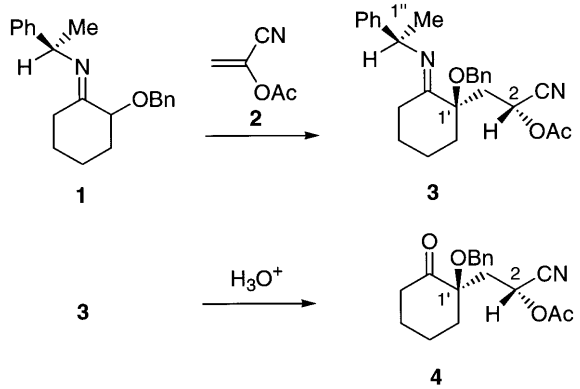
Unité Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université de Paris Sud, 5, rue J.-B. Clément, 92296 Châtenay-Malabry, France

Received 8 October 2000; accepted 30 October 2000

Abstract—The asymmetric Michael addition reaction between a variety of chiral imines and 2-acetoxyacrylonitrile, an electrophile equivalent to acetaldehyde, was reported. The resulting adducts were obtained in fair yields and with de and ee $\geq 95\%$.

The asymmetric Michael reaction using chiral imines under neutral conditions constitutes one of the most potent methodologies for the enantioselective elaboration of quaternary carbon centers.[1] As a part of our effort at synthesizing the side-chains of *Cephalotaxus* alkaloids,[2] we recently envisioned to extend the scope of the above reaction by the use, as an electrophilic partner, of a synthon equivalent to acetaldehyde. Reported herein is the utilization, for such a purpose, of 2-acetoxyacrylonitrile (**2**).

The reactivity of **2** towards chiral imine **1**, an adequate nucleophilic partner for the synthesis of the aforementioned targets,[2] was examined first. Addition of known imine **1** [prepared from 2-benzyloxycyclohexanone and (*R*)-1-phenylethylamine][3] to 2-acetoxyacrylonitrile (**2**)[4] (neat, 40 h at 20°C) gave adduct (2*R*,1′*R*,1″*R*)-**3**, *which turned out to be stereochemically homogeneous by ^1H and ^{13}C NMR spectroscopy*.[5] Hydrolysis of crude **3** (AcOH, H_2O, THF, 4 h at 20°C) next afforded cyclohexanone (2*R*,1′*R*)-**4**[6] (72% overall yield, calculated from the starting 2-benzyloxycyclohexanone). The de and ee in **4** were both $\geq 95\%$ (determined by ^1H NMR spectroscopy, having added Eu(fod) and $Eu(hfc)_3$ as shift reagents). The relative configuration of the two stereogenic centers in **4** was assigned by NMR spectroscopy including NOE experiments at level of the bicyclic derivatives **5** and **11**; the absolute configuration at C-1′ in **3** and **4** rests on a heuristic stereochemical rule we have proposed in this series (vide infra) (Scheme 1).



Scheme 1.

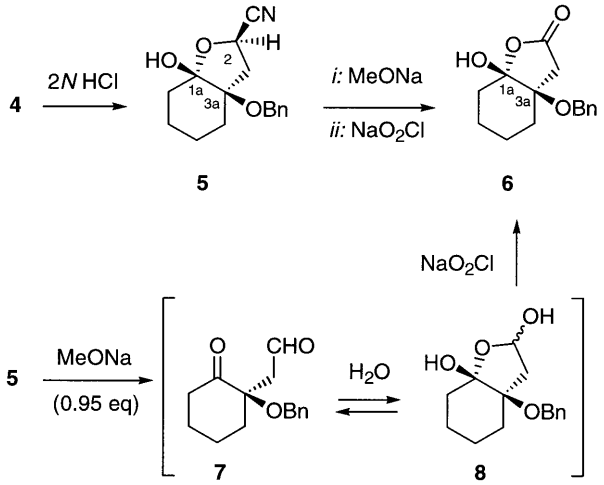
Regeneration of an aldehyde function at C-2 in **4** was next attempted. This requires a desacetylation step, followed by dehydrocyanation of the resulting cyanohydrin. While basic treatments of **4** furnished invariably undefined compounds, the bicyclic hemiacetal (2*R*,1a*S*,3a*R*)-**5**[7] was formed with a 77% yield when the reaction was conducted under acidic conditions (2N HCl, THF, 30 h at 50°C). However, all efforts at generating the aldehyde **7** through dehydrocyanation of **5** (a process which, in fact, would implicate the open form of this hemiacetal) were fruitless. In contrast,

Keywords: chiral imines; Michael reactions; 2-acetoxyacrylonitrile; stereocontrol.

* Corresponding authors. E-mail: francoise.dumas@cep.u-psud.fr; jean.dangelo@cep.u-psud.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(00)01971-7

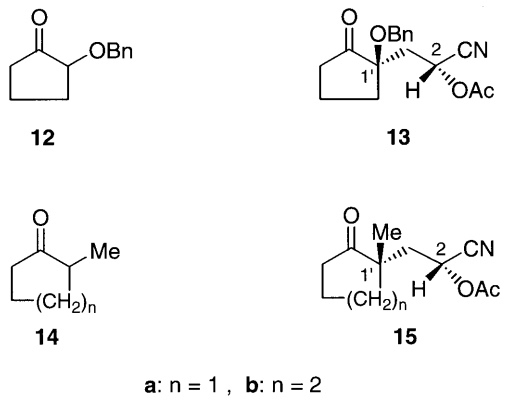
sequential exposure of **5** to NaOMe (0.95 equiv., MeOH, −20°C) and NaO_2Cl (NaH_2PO_4, H_2O, 20°C)[8] gave the sensitive bicyclic lactone (1a*S*,3a*R*)-**6**,[9] albeit with a modest yield (ca. 35%). Formation of **6** clearly involves the transient aldehyde **7**, in equilibrium through the addition of a molecule of water with the bis-hemiacetal **8**, the in situ oxidation of the latter furnishing ultimately the lactone **6** (Scheme 2).



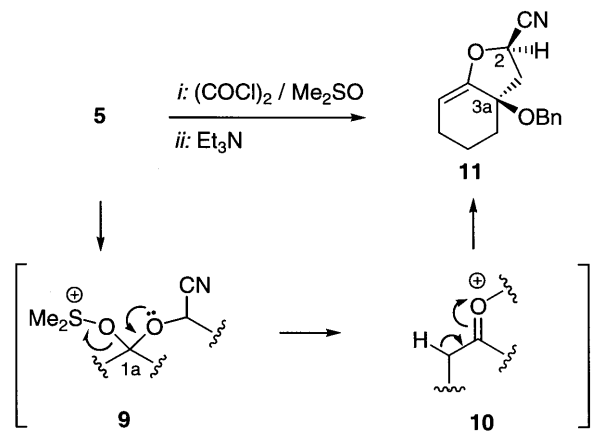
Scheme 2.

Incidentally, another interesting observation was made when compound **5** was subjected to the Swern reagent [DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N, 20°C]: the olefinic derivative (2*R*,3a*R*)-**11**[10] was isolated in a 55% yield. This apparently unprecedented dehydration process can be interpreted by assuming the original formation of a dimethylalkoxysulfonium ion[11] at C-1a, **9**, which collapses to olefin **11**, a fragmentation assisted by the neighboring oxygen atom and which likely implicated the intermediary oxonium ion **10**. An alternative route for converting **5** into **11** was also investigated, that employed the Burgess' inner salt ($Et_3N^+SO_2N^-COOMe$)[12] as a dehydration reagent (toluene, 48 h at 60°C, 60% yield) (Scheme 3).

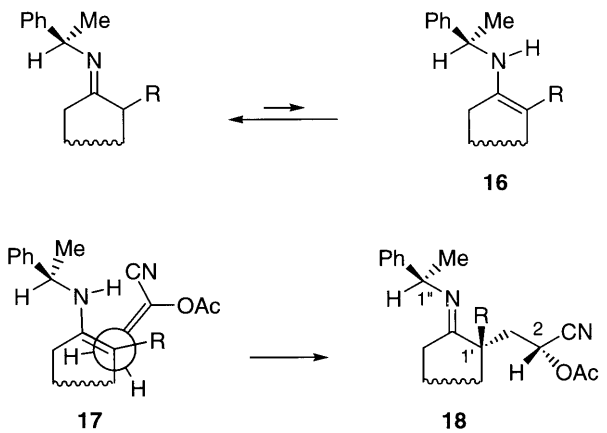
Finally, the versatility of the present conjugate addition was examined. Interestingly, we found that this reaction tolerates substantial variations on the starting cyclanone, both of the size of the ring and of the nature of the α-substituent. Thus, condensation of imines derived from cyclanones **12**, **14a**, **14b** and (*R*)-1-phenylethylamine with electrophilic alkene **2** paralleled completely the conversion (**1** → **4**): adducts (2*R*,1′*R*)-**13**, (2*R*,1′*S*)-**15a** and (2*R*,1′*S*)-**15b** were indeed, respectively, obtained in fair yields and with de and ee ≥ 95%.[13]



The nucleophilic species involved in the present Michael addition are in fact the more substituted secondary enamines **16**, in tautomeric equilibrium with the starting imines.[14] The above remarkable stereochemical outcomes can be rationalized by evoking the *synclinal* approach (**17**) of the two reactants [**16**+**2**]. According to this model, the alkylation process takes place preferentially on the less hindered π-face of the enamine (*anti* to the bulky phenyl group), portrayed in its energetically preferred conformation. This accounts for the absolute configuration at C-1′ in resulting adducts **18**. Control of the stereogenic center at C-2 in **18** originates from a concerted transfer of the NH proton of enamine **16** to the α-vinylic center of electrophile **2**, the electron-withdrawing group of this acceptor facing the nitrogen atom of the enamine ('*endo*-arrangement'). It is noteworthy that the present stereochemical pattern is in all respects identical to the one evoked when methyl 2-acetoxyacrylate was used as an electrophilic partner (Scheme 4).[14a,c]



Scheme 3.



Scheme 4.

Work on the utilization of adduct **4** and analogs as starting materials for the enantioselective synthesis of the side-chains of *Cephalotaxus* alkaloids is in progress in our laboratory.

Acknowledgements

We are grateful to Dr. Jacqueline Mahuteau for valuable assistance with NMR studies and Mrs. Sophie Mairesse-Lebrun for performing elemental analyses (Centre d'Etudes Pharmaceutiques Châtenay-Malabry).

References

1. For recent references, see: (a) Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2015–2021; (b) Nour, M.; Tan, K.; Cavé, C.; Villeneuve, D.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **2000**, *11*, 995–1002; (c) Gassama, A.; d'Angelo, J.; Cavé, C.; Mahuteau, J.; Riche, C. *Eur. J. Org. Chem.* **2000**, 3165–3169.
2. de Oliveira, E. R.; Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **1997**, *38*, 3723–3726.
3. Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.* **1989**, *30*, 345–348.
4. Nowak, R. M. *J. Org. Chem.* **1963**, *28*, 1182–1187.
5. Compound **3**: colorless oil; IR (neat): 2233, 1752, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 1.39 (d, $J = 6.5$ Hz, 3H), 1.32–2.48 (m, 8H), 1.98 (s, 3H), 2.45 (dd, $J = 6.2$, 15.4 Hz, 1H), 2.79 (dd, $J = 5.4$, 15.4 Hz, 1H); 4.00 (d, $J = 11.7$ Hz, 1H), 4.36 (d, $J = 11.7$ Hz, 1H), 4.74 (q, $J = 6.5$ Hz, 1H), 5.55 (dd, $J = 5.4$, 6.2 Hz, 1H), 7.07–7.45 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 20.1 (CH_3), 20.6 (CH_2), 25.3 (CH_3), 25.8 (CH_2), 27.0 (CH_2), 36.2 (CH_2), 37.1 (CH_2), 58.2 (CH), 58.4 (CH), 63.9 (CH_2), 79.6 (C), 118.1 (C), 126.4 (2 CH), 126.6 (CH), 126.7 (2 CH), 127.2 (CH), 128.1 (2 CH), 128.3 (2 CH), 138.0 (C), 145.8 (C), 168.8 (C), 169.7 (C) ppm.
6. Compound **4**: colorless solid; mp 62°C (EtOH); $[\alpha]_D^{20} = +75$ ($c = 2$, EtOH); IR (KBr): 2240, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.51–1.64 (m, 4H), 1.99 (s, 3H), 2.12 (m, 1H), 2.21 (dd, $J = 7.1$, 15.7 Hz, 1H), 2.27–2.40 (m, 2H), 2.67 (dd, $J = 5.4$, 15.7 Hz, 1H), 2.77 (ddd, $J = 4.9$, 12.2, 12.8 Hz, 1H), 4.17 (d, $J = 11.1$ Hz, 1H), 4.53 (d, $J = 11.1$ Hz, 1H), 5.43 (dd, $J = 5.4$, 7.1 Hz, 1H), 7.28–7.44 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 20.2 (CH_3), 20.4 (CH_2), 27.7 (CH_2), 34.3 (CH_2), 37.5 (CH_2), 39.1 (CH_2), 57.3 (CH), 65.4 (CH_2), 81.3 (C), 117.1 (C), 127.1 (2 CH), 127.7 (CH), 128.5 (2 CH), 136.8 (C), 169.0 (C), 211.0 (C) ppm; anal. calcd: C, 68.54; H, 6.71; N, 4.44; found: C, 68.66; H, 6.81; N, 4.36.
7. Compound **5**: colorless solid; mp 105°C (CH_2Cl_2); $[\alpha]_D^{20} = +17$ ($c = 3$, $CHCl_3$); IR (KBr): 3545, 2235 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 1.31–1.74 (m, 5H), 1.80 (m, 2H), 2.01 (m, 1H), 2.39 (dd, $J = 8.6$, 12.6 Hz, 1H), 2.64 (dd, $J = 5.2$, 12.6 Hz, 1H), 3.73 (s, 1H, OH), 4.47 (d, $J = 10.6$ Hz, 1H), 4.57 (d, $J = 10.6$ Hz, 1H), 4.71 (dd, $J = 5.2$, 8.6 Hz, 1H), 7.28–7.39 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 21.0 (CH_2), 22.3 (CH_2), 29.9 (CH_2), 33.5 (CH_2), 36.8 (CH_2), 62.0 (CH), 66.1 (CH_2), 81.3 (C), 105.0 (C), 119.4 (C), 127.9 (2 CH), 128.4 (3 CH), 137.3 (C) ppm; anal. calcd: C, 70.31: H, 7.01: N, 5.12; found: C, 70.25; H, 7.03; N, 5.02.
8. Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176.
9. Compound **6**: sensitive white solid; IR (KBr): 3383, 1769 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 1.09–1.95 (m, 5H), 2.01–2.47 (m, 3H), 2.68 (d, $J = 17.1$ Hz, 1H), 2.85 (d, $J = 17.1$ Hz, 1H), 4.38 (d, $J = 10.1$ Hz, 1H), 4.50 (d, $J = 10.1$ Hz, 1H), 4.71 (s, 1H, OH), 7.18–7.42 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 21.6 (CH_2), 22.0 (CH_2), 29.4 (CH_2), 34.9 (CH_2), 36.9 (CH_2), 65.1 (CH_2), 81.2 (C), 106.7 (C), 127.7 (2 CH), 128.2 (CH), 129.0 (2 CH), 136.9 (C), 171.8 (C) ppm.
10. Compound **11**: colorless solid; mp 107°C (EtOH); $[\alpha]_D^{20} = -147$ ($c = 0.7$, $CHCl_3$); IR (KBr): 3038, 2233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.34 (dt, $J = 3.5$, 13.8 Hz, 1H), 1.72 (m, 1H), 1.84 (m, 1H), 2.02–2.13 (m, 2H), 2.23 (m, 1H), 2.51 (dt, $J = 3.5$, 13.8 Hz, 1H), 2.85 (d, $J = 13.6$ Hz, 1H), 4.49 (d, $J = 10.3$ Hz, 1H), 4.58 (d, $J = 10.3$ Hz, 1H), 4.99 (d, $J = 8.2$ Hz, 1H), 5.12 (t, $J = 3.8$ Hz, 1H), 7.27–7.46 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 17.3 (CH_2), 22.9 (CH_2), 30.1 (CH_2), 39.4 (CH_2), 64.7 (CH), 66.3 (CH_2), 77.5 (C), 99.8 (CH), 118.3 (C), 127.6 (2 CH), 128.4 (3 CH), 137.5 (C), 154.1 (C) ppm.
11. Omura, K.; Swern, D. *Tetrahedron* **1978**, 1651–1660.
12. Burgess, E. M.; Penton, Jr., H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.
13. Compound **13**: 55% yield, $[\alpha]_D^{20} = +46$ ($c = 0.8$, EtOH); compound **15a**: 60% yield, $[\alpha]_D^{20} = +31$ ($c = 5.5$, EtOH); compound **15b**: 74% yield, $[\alpha]_D^{20} = +65$ ($c = 4.5$, EtOH).
14. For the mechanistic aspects, see: (a) Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35*, 9705–9708; (b) Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361–4368; (c) Cavé, C.; Le Porhiel-Castellon, Y.; Daley, V.; Riche, C.; Chiaroni, A.; d'Angelo, J. *Tetrahedron Lett.* **1997**, *38*, 8703–8706; (d) Tran Huu Dau, M. E.; Riche, C.; Dumas, F.; d'Angelo, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1059–1064.