Pergamon

Tetrahedron Letters 42 (2001) 4779–4781

TETRAHEDRON LETTERS

First intramolecular geminal acylation: synthesis of bridged bicyclic diketones

Angela N. Blanchard and D. Jean Burnell*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

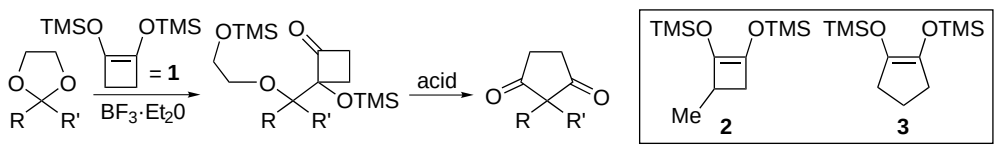
Received 23 February 2001; accepted 18 May 2001

Abstract—Bicyclic diketones have been produced by Lewis acid-promoted geminal acylations involving cyclic acyloins tethered to an acetal. This intramolecular process must proceed via a mode of reaction which, due to steric hindrance, is not seen in the intermolecular version of the geminal acylation.

Considerable effort has gone into the development of procedures for the conversion of acetals[1–3] and ketones[4] into cyclic 1,3-diketones by geminal acylation with a cyclic acyloin such as 1,2-bis(trimethyl-silyloxy)-cyclobutene (**1**),[5] its methylated analogues (e.g. **2**)[6,7] and 1,2-bis(trimethylsilyloxy)cyclopent-ene (**3**).[8] Geminal acylation has been used as a key-step in syntheses of natural products and other structurally interesting compounds.[9] The two-step process to generate a 1,3-cyclopentanedione with **1** is illustrated in Scheme 1. In many instances, both steps can take place in the same vessel, without the addition of trifluoroacetic acid (TFA), if many equivalents of $BF_3{\cdot}Et_2O$ are used initially. However, in the presence of a high concentration of the Lewis acid, **1**, **2** and **3** also decompose quite quickly to leave intractable polar material, so the one-pot procedure often requires an excess of the acyloin in order to give a good yield of the cyclic diketone.[2,3] Steric hindrance greatly affects the yields, so the efficacy of the overall process ranges from zero to quantitative. Reactions with **3** are slower than with **1**, but some 1,3-cyclohexanediones can be obtained in excellent yields by the one-pot procedure.[8]

The intramolecular reaction of an acetal tethered to an acyloin has never been reported. Such a geminal acylation might be strongly disfavored for two reasons. Firstly, unless the tether were long, the initial carbon–carbon bond-forming reaction would involve reaction at the carbon of the acyloin adjacent to the tether and onto the face of the acyloin *syn* to the tether. However, in reactions of **2**, the one mode of addition that is never seen is onto the carbon adjacent to, and *syn* to, its methyl substituent.[6] This is certainly due to a severe steric interaction. Secondly, bridged bicyclic diketones such as those expected by the acid-promoted geminal acylation, are susceptible to acid-promoted ring-opening.[10,11]

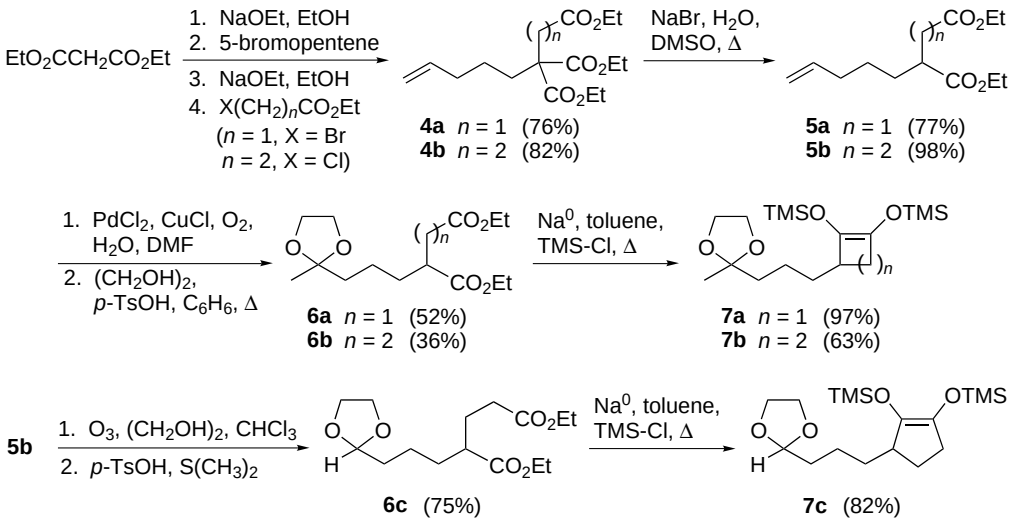
We set out to assess the feasibility intramolecular geminal acylation with acetals derived from both a ketone and an aldehyde and with four- and five-membered acyloins. Tethers of three carbons were employed. The preparation of the substrates **7a–c** is outlined in Scheme 2. Alkylation of diethyl malonate, first with 5-bromo-pentene and then with a halo-ester, yielded the triesters **4a**,**b**. Decarboxylation of one of the geminal carboxyethyl groups using sodium bromide and water in DMSO[12] gave **5a**,**b**. Wacker oxidation[13] provided methyl ketones that were converted to the acetals **6a**,**b**. Acyloin reactions with sodium metal in toluene gave



Scheme 1. Geminal acylation reaction.

* Corresponding author. Tel.: (709) 737-8535; fax: (709) 737-3702; e-mail: jburnell@mun.ca

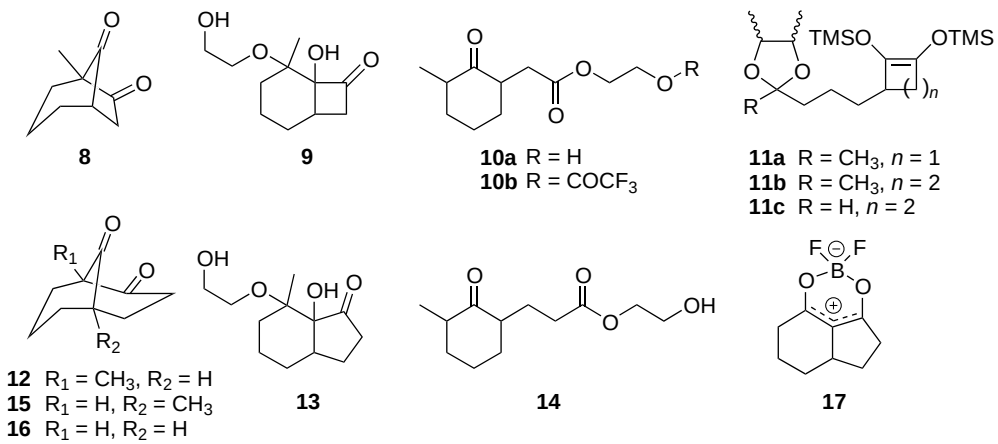
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00852-8



Scheme 2. Synthesis of substrates for intramolecular geminal acylation.

7a,**b**. Attempts to purify **7a**,**b** by distillation were compromised by their thermal instability, and their sensitivity to moisture precluded other methods of purification. Nevertheless, the ^{1}H NMR spectra of the crude reaction products indicated that the ester functions were gone and each product had two trimethylsilyl groups. The yields for the acyloin steps were estimated from these ^{1}H NMR spectra. Diester **5b** was treated with ozone in the presence of ethanediol, and, after 20 minutes, a small amount of *p*-TsOH was added with dimethylsulfide. This provided the acetal **6c**, and an acyloin reaction gave **7c**, which could also not be purified rigorously.

A dilute toluene solution of **7a** was cooled to −78°C before 15 equivalents of $BF_3{\cdot}Et_2O$ were added. After stirring for 7.5 h, the mixture was allowed to warm slowly to room temperature. Aqueous work-up provided 16% of the bicyclo[3.2.1]octanedione **8**,[15] along with small amounts of **9** (as a single isomer) and **10a**. Compound **9** was an intermediate, unrearranged molecule, and **10a** arose by acid-induced ring-opening of **8**. The initial aldol process took place to a modest extent, but the production of a considerable amount of polar material indicated that the acyloin moiety was also being destroyed relatively quickly. Furthermore, some by-products appeared to be formed by attack on the solvent (toluene). With much less $BF_3{\cdot}Et_2O$, **9** still produced, but diketone **8** was not detected. In order to effect the rearrangement of **9** to **8**, TFA was added. The overall yield of **8** was not improved, but **10b** was an additional minor product. A problem with ring-opening had been seen with 1,3-cyclopentane-dione products formed by geminal acylation from more hindered acyclic ketones.[3] (Ring-opening can be greatly encouraged by the use of $SnCl_4$ as the Lewis acid.[1,14]) Nevertheless, when the substrate for the geminal acylation was an acetal derived from 2,3-butanediol, ring opening was suppressed.[3] Therefore, acyloin **11a** was prepared as for **7a** (acyloin estimated at 82% yield). Two equivalents of $BF_3{\cdot}Et_2O$ were added slowly to a dichloromethane solution of **11a** at −78°C. When the last of the $BF_3{\cdot}Et_2O$ was added, the solution was warmed to room temperature and TFA (10 equiv.) was introduced. Work-up after one hour provided **8** in an improved yield of 36% following chromatography. There was no evidence of any ring-opened product by ^{1}H NMR.



In the presence of 15 equivalents of $BF_3{\cdot}Et_2O$, the acyloin **7b** (in toluene, −78°C warming to room temperature overnight) provided the bicyclo[3.3.1]nonanedione

12[16] in a yield of 23%. (None of the unrearranged aldol product **13** was detected.) The only isolated by-product (25%) was the ring-opened compound **14** (as a 2:1 mixture of isomers), but the use of the more substituted acetal **11b** did not lead to a better yield of **12**. Butkus and Bielinyte–Williams[11] had shown that **12** can also be produced by the reaction of the enamine of 2-methylcyclohexanone with acryloyl chloride, but this unavoidably leads to the production of an equal amount of **15**. (Furthermore, it appears from their ^{13}C NMR data that their assignment of structures to the isomers **12** and **15** might be reversed.)

The addition of $BF_3{\cdot}Et_2O$ to a dilute solution of **7c**, in which the acetal was produced from an aldehyde, did not give any of the desired bicyclic ketone **16**. The unusual fused tricyclic compound **17**,[17] in which a boron from the Lewis acid was captured in one ring, was isolated in low yield (18%).

In summary, intramolecular geminal acylation can take place when a four- or a five-membered acyloin is attached by a three-carbon tether to the acetal derived from a methyl ketone. This is in spite of the initial step involving a mode of reaction (carbon–carbon bond-formation adjacent to, and *syn* to, the point of attachment of the tether onto the acyloin) that is highly disfavored in the analogous, intermolecular reactions of **2**. Although the yields of the bicyclic diketones were modest, the positions of the methyl groups on the bridgeheads were assured by the intramolecular geminal acylation process, in contrast with the enamine route.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

References

1. Shimada, J.; Hashimoto, K.; Kim, B. M.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.
2. (a) Burnell, D. J.; Wu, Y.-J. *Tetrahedron Lett.* **1988**, *29*, 4369; (b) Pandey, B.; Khire, U. R.; Ayyangar, N. R. *Synth. Commun.* **1989**, *19*, 2741.
3. Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311.
4. Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485.
5. Bloomfield, J. J.; Nelke, J. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp. 167–172.
6. Crane, S. N.; Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722.
7. (a) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352; (b) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708.
8. Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1989**, *30*, 1021.
9. For instance: (a) Parker, K. A.; Koziski, K. A.; Breau, G. *Tetrahedron Lett.* **1985**, *26*, 2181; (b) Bunnelle, W. H.; Shangraw, W. R. *Tetrahedron* **1987**, *43*, 2005; (c) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1989**, *67*, 816; (d) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804; (e) Hyuga, S.; Shoji, H.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2303; (f) Julia, M.; Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C. *Bull. Soc. Chim. Fr.* **1993**, *130*, 447; (g) Pandey, B.; Reddy, R. S.; Kumar, P. *J. Chem. Soc., Chem. Commun.* **1993**, 870; (h) Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104; (i) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921; (j) Liu, P.-Y.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1183; (k) Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337; (l) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345; (m) Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3295; (n) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335; (o) Liu, P.-Y.; Wu, Y.-J.; Burnell, D. J. *Can. J. Chem.* **1997**, *75*, 656; (p) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1998**, 1755.
10. Hickmott, P. W.; Hargreaves, J. R. *Tetrahedron* **1967**, *23*, 3151.
11. Butkus, E.; Bielinyte-Williams, B. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1343.
12. Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.
13. Tsuiji, J.; Masaoka, K.; Takahashi, T. *Tetrahedron Lett.* **1977**, *26*, 2267.
14. Kuwajima, I.; Azegami, I. *Tetrahedron Lett.* **1979**, *24*, 2369.
15. For **8**: white solid, mp 65–66°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (1H, m), 2.66 (2H, m), 2.20 (2H, m), 1.88 (4H, m), 1.06 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.7, 212.3, 59.3, 45.7, 44.9, 42.9, 35.7, 18.2, 12.1.
16. For **12**: white solid, ^1H NMR (500 MHz, $CDCl_3$) δ 2.90 (1H, m), 2.64 (1H, m), 2.38 (1H, m), 2.27 (1H, m), 2.20 (1H, m), 2.07 (2H, m), 1.81 (1H, m), 1.75–1.60 (3H, m), 1.15 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 212.6, 63.4, 44.5, 43.2, 39.1, 36.1, 22.0, 19.3, 16.8.
17. For **17**: white solid, mp 98–100°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.91 (2H, m), 2.55 (3H, m), 2.13 (2H, m), 1.72 (2H, m), 1.30–0.80 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 186.2, 116.6, 36.0, 33.7, 31.0, 30.1, 30.0, 21.9. The structure of **17** was confirmed by X-ray diffraction.