Mendeleev Commun., 2004, 14(6), 296–297

The conversion of achiral molecules in chiral crystals to chiral molecules

Nicie Conley,[a] Robert N. Compton[a,b] and Richard M. Pagni*[a]

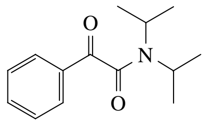
[a] *Department of Chemistry, University of Tennessee, Knoxville, TN 37996, USA. E-mail: rpagni@utk.edu*
[b] *Department of Physics, University of Tennessee, Knoxville, TN 37996, USA*

DOI: 10.1070/MC2004v014n06ABEH002010

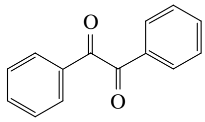
***N*,*N*-Diisopropylbenzoylformamide, benzil, and 4,4′-dimethylchalcone are achiral molecules that crystallize in chiral space groups. It is possible with suitable reagents in water to convert these molecules in the crystals directly into chiral molecules. In the case of the chalcone asymmetric induction in its reaction is observed.**

When sodium chlorate, an achiral ionic compound crystallizing in the chiral space group $P2_13$,[1] is crystallized from water while being exposed to very energetic circularly polarized electrons and positrons, the resulting crystals show significant preference for one enantiomer over the other.[2,3] The chiral electrons afford an excess of (+) crystals while the positrons, which have the opposite helicity, afford an excess of (–) crystals. The enantiomeric excess of the sodium chlorate crystals is easily measured by polarimetry.[2]

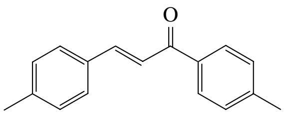
We wanted to see what effect the chiral particles and other perturbations had on the crystallization of achiral organic molecules which, just as sodium chlorate, crystallize in chiral space groups. Because many of these crystals are birefringent, polarimetry cannot be used to analyze the crystals; an alternate procedure is required. A well-established procedure is to convert molecules in the crystal directly into chiral molecules using a suitable chemical reaction.[4] The biphasic reaction hopefully will result in asymmetric induction, yielding an optically active molecule whose activity could be deduced by polarimetry. We have found water to be a suitable solvent because the majority of organic crystals are insoluble in this medium. The molecules chosen for this study were *N*,*N*-diisopropylbenzoylformamide **1**, benzil **2** and 4,4′-dimethylchalcone **3**.



1



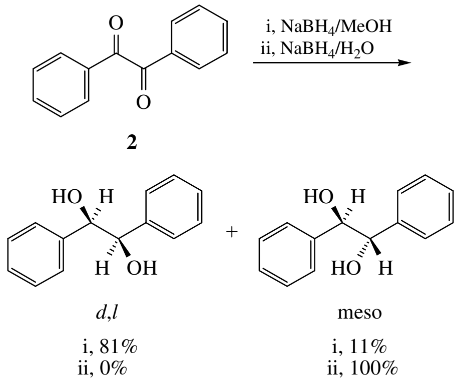
2



3

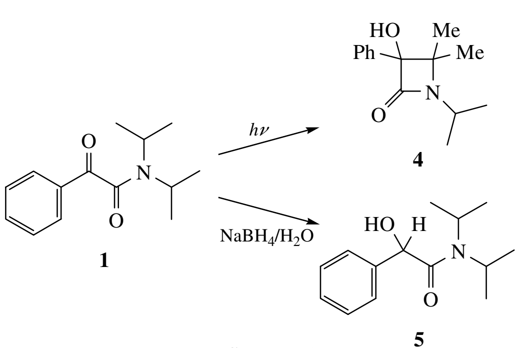
Benzil **2** crystallizes in the chiral space group $P3_12_1$.[5] The molecule is easily reduced in methanol to yield a mixture of meso (81%) and *d*,*l* (11%) 1,2-diphenylethane-1,2-diol (Scheme 1).[6] When crystalline benzil is slurried with a solution of sodium borohydride in water, a rapid reaction ensues yielding the meso diol exclusively. Because the meso compound has no optical activity, this procedure cannot be used to convert the chirality of the benzil crystals into molecular chirality.

N,*N*-Diisopropylbenzoylformamide **1**, which is prepared by the reaction of the acid chloride of benzoylformic acid with diisopropylamine,[7] crystallizes in the chiral space group $P2_12_12_1$.[8] When the crystalline solid is photolyzed, it undergoes a Norrish II reaction to yield chiral lactam **4** in high chemical and optical yields (Scheme 2).[8–12] Because the photoreaction in our hands was very slow (Rayonet Reactor – 4 2537 Å lamps, 35 W per lamp), we sought an alternate method of asymmetric induction. When **1** is reduced with sodium borohydride in methanol, chiral but racemic hydroxyformamide **5**[13,14] is generated in 90% yield after 20 min. When crystalline compound **1** is slurried with sodium borohydride in water, **5** is also generated, but slowly (Scheme 2). After two hours at room temperature, the reaction was 50% complete; little additional reaction occurred after another twelve hours. The alternate method thus works but because its reaction is also slow it is no better than the photochemical procedure as a method of asymmetric induction.



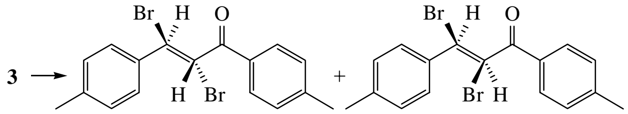
Scheme 1

4,4′-Dimethylchalcone **3**, which is readily prepared in copious amounts by the aldol condensation of *p*-methylbenzaldehyde with *p*-methylacetophenone,[15] crystallizes in the $P2_12_12_1$ space group.[16] The effect of stirring and β particles on the crystallization of **3** from ethyl acetate has been examined by Durand *et al.*[15] and Sullivan *et al.*[17] using a bromination reaction and polarimetry. Bromination of **3** in methylene chloride affords an 86:14 mixture of *erythro* and *threo* dibromides formed by *anti* and *syn* addition of bromine across the C–C double bond.[18] Bromination of crystalline compound **3** with bromine vapor is reported to yield the *erythro* product exclusively,[19,20] with some asymmetric induction occurring in the reaction. In our hands, however, the reaction of bromine vapor afforded both the *erythro* and *threo* products (Scheme 3). An alternate procedure developed by Toda and coworkers[18] alleviated this problem. Treatment of **3** with pyridinium tribromide in a water slurry generates the *erythro* adduct exclusively.[†] Depending on how chalcone **3** was treated during its crystallization, it yields the *erythro* dibromide with specific rotations as large as 37°. Because the pure enantiomer of the dibromide has a specific rotation of 167°,[19] the asymmetric induction during the bromination in



Scheme 2

Mendeleev Commun., 2004, 14(6), 296–297



3 **3**

erythro *threo*

Br_2/CH_2Cl_2	86	:	14
Pyridinium tribromide/H_2O	100	:	0

Scheme 3

water is at least 22%. The largest specific rotation obtained when crystalline chalcone was brominated with bromine vapor was 14°, corresponding to an asymmetric induction of 8%.[15]

In conclusion, we have shown that one can convert achiral *N*,*N*-diisopropybenzoylformamide **1**, benzil **2**, and 4,4′-dimethylchalcone **3** in their chiral crystalline phases into chiral molecules by suitable heterogeneous reactions in water. Compound **2** yields a meso product on reduction with sodium borohydride, while **1** reacts slowly with the same reducing reagent. Compound **3** reacts rapidly with pyridinium tribromide to give a single product with sufficient optical activity to make the study of the crystallization of **3** easy to perform.[‡]

This research was supported by the National Science Foundation.

References

1 S. C. Abrahams and J. L. Bernstein, *Acta Crystallogr.*, 1977, **B33**, 3601.

2 S. Mahurin, M. McGinnis, J. S. Bogard, L. D. Hulett, R. M. Pagni and R. N. Compton, *Chirality*, 2001, **13**, 636.

3 R. M. Pagni and R. N. Compton, *Cryst. Growth Design*, 2002, **2**, 249.

4 *Organic Solid-State Reactions*, ed. F. Toda, Kluwer, Dordrecht, 2002.

5 M. More, G. Odou, and J. Lefebvre, *Acta Crystallogr.*, 1987, **B43**, 398.

6 J. Dale, *J. Chem. Soc. (Abstracts)*, 1961, 910.

7 H. Aoyama, M. Sakamoto, K. Kuwabara, K. Yoshida and Y. Omote, *J. Am. Chem. Soc.*, 1983, **105**, 1958.

8 A. Sekine, K. Hori, Y. Ohashi, M. Yagi and F. Toda, *J. Am. Chem. Soc.*, 1989, **111**, 697.

9 H. Aoyama, T. Hasegawa and Y. Omote, *J. Am. Chem. Soc.*, 1979, **101**, 5343.

10 F. Toda, M. Yagi and S. Soda, *J. Chem. Soc., Chem. Commun.*, 1987, 1413.

11 F. Toda and H. Miyamoto, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1129.

12 T. Asahi, M. Nakamura, J. Kobayashi, F. Toda and H. Miyamoto, *J. Am. Chem. Soc.*, 1997, **119**, 3665.

13 F. Toda, K. Kiyoshige and M. Yagi, *Angew. Chem., Int. Ed. Engl.*, 1989, **101**, 329.

14 A. S. Fletcher, K. Smith and K. Swaminanthan, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1881.

15 D. J. Durand, D. K. Kondepudi, D. O. Moreira, Jr. and F. H. Quina, *Chirality*, 2002, **14**, 284.

16 D. Rabinovich and H. Hope, *Acta Crystallogr.*, 1980, **A36**, 670.

17 R. Sullivan, N. Conley, R. N. Compton and R. M. Pagni, *Mendeleev Commun.*, 2003, 131.

18 K. Tanaka, R. Shiraishi and F. Toda, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3069.

19 K. Penzien and G. M. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 608.

20 E. Hadjoudis, *Mol. Cryst. Liq. Cryst.*, 1986, **134**, 237.

Received: 10th September 2004; Com. 04/2335

[†] The *erythro* dibromide which we prepared had mp 156–157 °C. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, Me), 2.45 (s, 3H, Me), 5.65 (d, 1H, CH next to CO, *J* 11.3 Hz), 5.85, (d, 1H, CH next to Ar, *J* 11.3 Hz), 7.20 (d, 2H, Ar, *J* 8.1 Hz), 7.35 (d, 2H, Ar, *J* 8.2 Hz), 7.45 (d, 2H, Ar, *J* 8.1 Hz), 8.00 (2H, Ar, *J* 8.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.3 (Me), 21.8 (Me), 46.9 (CH), 50.1 (CH), 128.2 (Ar), 129.0 (Ar), 129.5 (Ar), 129.7 (Ar), 131.9 (Ar), 135.4 (Ar), 139.3 (Ar), 145.3 (Ar), 190.6 (CO).

[‡] Our research on the effect of intense polarized 1064 nm light on the crystallization of **3** will be reported elsewhere.