Synthesis of 1,3-Dioxin-4-ones having a Trifluoromethyl Group at the 5-Position: Versatile Building Blocks for Trifluoromethylated Compounds

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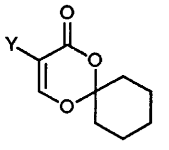
The reaction of 5-iodo-1,3-dioxin-4-ones with trifluoromethyl iodide in the presence of copper powder in hexamethylphosphoric triamide affords the title compounds, which can be converted either to α-trifluoromethylated β-keto acid derivatives or to uracil or oxazine derivatives bearing a trifluoromethyl group.

We have recently synthesized 5-fluoro-1,3-dioxin-4-ones and utilized them as building blocks for monofluorinated derivatives either of formylacetic acid or of heterocyclic systems.[1] Since introduction of trifluoromethyl groups into a variety of organic molecules is important, as is introduction of fluorine[2] in fluorine chemistry, much effort has been expended in elaboration of trifluoromethylation methods.[3] We now report the synthesis of 5-trifluoromethyl-1,3-dioxin-4-ones and some of their reactions.

When the 5-iodo-1,3-dioxin-4-ones **1b**, **2b** and **3b**, synthesized from the 5-unsubstituted dioxinones **1a**, **2a** and **3a** by our procedure,[1,4] were allowed to react with trifluoromethylcopper in hexamethylphosphoric triamide[5] (*ca.* 50 °C), the corresponding trifluoromethylated derivatives **1c** (m.p. 77.5–78.0 °C) **2c**: (oil) and **3c** (m.p. 160–161 °C)†‡ were obtained in satisfactory yields (*ca.* 65%). Small amounts (*ca.* 5–10%) of the pentafluoroethyl derivatives **1d** (oil) and **2d** (m.p. 64.0–64.5 °C) as well as the 5-unsubstituted derivative **1a** were obtained concomitantly. It is obvious that the former compounds have been formed by coupling of the pentafluoroethyl complex generated from the trifluoromethyl complex[6] and **1a** was formed by reduction with copper powder present in the reagent.[7]

The following transformations using **1c**, **2c** and **3c** have demonstrated that these dioxinones serve *via* the ring-opened ketene species (**A**) either as the equivalents of β-keto acids or the precursors of uracils and oxazinones having a trifluoromethyl group. Thus, reaction of **2c** with dimethylcyanamide in refluxing xylene gave the expected oxazinone **5** (m.p. 90–91.5 °C)‡ in 81% yield.§ In the same manner, the oxazinone **4** (m.p. 113–114 °C) and **6** (m.p. 185–186 °C) were obtained from **1c** and **3c**, respectively. The reaction of **1c** with 1,3-dimethylurea in refluxing toluene led to the corresponding uracil **7** (m.p. 108–109 °C)‡[8] in 84% yield.

The introduction of a trifluoromethyl group at an aliphatic carbon atom is more difficult than bonding trifluoromethyl to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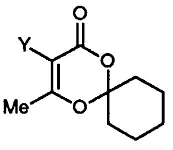
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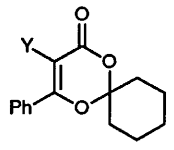
a; Y = H
b; Y = I
c; Y = CF_3
d; Y = C_2F_5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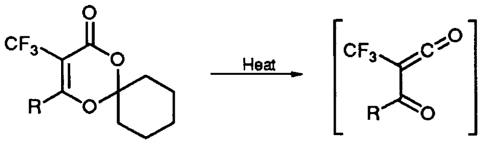
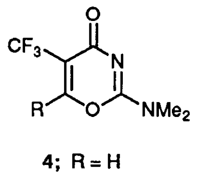
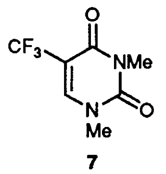


1c-3c
A


4; R = H
5; R = Me
6; R = Ph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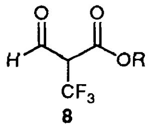
† All new compounds exhibited satisfactory spectroscopic (NMR and IR) and combustion or high resolution mass spectral analytical data.

‡ **1c**: ^1H NMR ($CDCl_3$) δ: 1.2–2.3 (10H, m, 5 × CH_2), 7.70 (1H, s, 6-H). **2c**: ^1H NMR ($CDCl_3$) δ: 1.2–2.3 (10H, m, 5 × CH_2), 2.27 (3H, q, *J* 2 Hz, 6-H). **3c**: ^1H NMR ($CDCl_3$) δ: 1.2–2.3 (10H, m, 5 × CH_2), 7.55 (5H, s, Ph). **5**: ^1H NMR ($CDCl_3$) δ: 2.40 (3H, q, *J* 2 Hz, CH_3), 3.17 (6H, s, 2 × NCH_3). **7**: ^1H NMR ($CDCl_3$) δ: 3.37 (3H, s, CH_3), 3.50 (3H, s, CH_3), 7.70 (1H, s, 6-H). **9e** (keto/enol = *ca.* 9): ^1H NMR ($CDCl_3$) δ: 2.30 (3H, s, CH_3), 4.23 (1H × 0.9, q, *J* 8 Hz, 2-H), 5.27 (2H, s, CH_2), 7.37 (5H, s, Ph), 14.00 (1H × 0.1, s, OH).

§ This paper reports reactions using dioxinones having a spiro-linked pentamethylene chain at the 2-position; reactions of the corresponding 2,2-dimethyl derivatives proceeded similarly.



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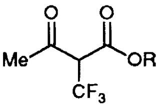

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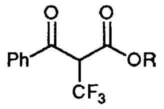

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e; R = CH_2Ph
f; R = Bu^t

an aromatic nucleus. The synthesis of α-trifluoromethylated β-keto esters is particularly difficult, because, under basic conditions, these α-trifluoromethylated compounds are readily dehydrofluorinated to give β,β-difluoroacrylic acid intermediates which are prone to hydrolysis and decarboxylation.[9] Though several methods[9–11] are available for the synthesis of these esters, there is a clear need for a new and general method. We have developed a simple one-pot synthesis of β-keto esters containing a trifluoromethyl group in the α-position using the dioxinones **1c, 2c** and **3c** as the starting materials. Thus, according to the general procedure for the conversion of the dioxinones to β-keto esters,[12] **2c** was refluxed in xylene containing benzyl alcohol to give the ester **9e** (oil)‡ in nearly quantitative yield. This reaction proceeded, irrespective of either the 6-substituent in the dioxinones (**1–3**) or the alcohols ($PhCH_2OH$ or Bu^tOH) to give the corresponding β-keto esters **8e, f, 9e, f**, and **10e, f**.

We are now studying the use of **1c, 2c** and **3c** in pericyclic (Diels–Alder[13] and photo[2 + 2]cycloaddition[14]) reactions,[15] in which the C–C double bond in the dioxinone ring is used without destroying the ring.

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References

1 M. Sato, C. Kaneko, T. Iwaoka, Y. Kobayashi and T. Iida, *J. Chem. Soc., Chem. Commun.*, 1991, 699.

2 The synthesis of fluorinated organic compounds as well as their novel physical and biological properties have been reviewed: *Biochemical Aspects of Fluorine Chemistry*, eds. R. Filler and Y. Kobayashi, Kodansha Ltd, Tokyo, 1982; J. T. Welch, *Tetrahedron*, 1987, **43**, 3125; T. B. Patrick, *J. Chem. Ed.*, 1979, **56**, 228.

3 I. Kumadaki, *Yakugaku Zasshi*, 1985, **105**, 713.

4 M. Sato, N. Yoneda and C. Kaneko, *Chem. Pharm. Bull.*, 1986, **34**, 4577.

5 The most useful trifluoromethylation reaction employs organometallic reagents, trifluoromethyl-copper or -zinc complexes and has wide applicability for aryl halides and related compounds: Y. Kobayashi, K. Yamamoto and I. Kumadaki, *Tetrahedron Lett.*, 1979, 4071; T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1982, 137.

6 The disproportionation of [CF_3Cu] to [CF_3CF_2Cu] was demonstrated by a spectroscopic study and by the formation of pentafluoroethylated products in trifluoromethylations using trifluoromethylcopper complexes: D. W. Wiemers and D. J. Burton, *J. Am. Chem. Soc.*, 1986, **108**, 832; Y. Kobayashi and I. Kumadaki, *J. Chem. Soc., Perkin Trans. 1*, 1980, 661.

7 Y. Kobayashi, K. Yamamoto, T. Asai, M. Nakano and I. Kumadaki, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2755.

8 K. Fuchikawa and I. Ojima, *Tetrahedron Lett.*, 1982, **23**, 4099; see also T. Fuchikami, A. Yamanouchi and I. Ojima, *Synthesis*, 1984, 766.

9 T. Yokozawa, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, 1984, **25**, 3987; T. Stephan, S. T. Purrington and C. L. Bumgardner, *J. Org. Chem.*, 1984, **49**, 3702 and references cited therein.

10 K. Uneyama and K. Ueda, *Chem. Lett.*, 1988, 853.

11 T. Yokozawa, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, 1984, **25**, 3991.

12 Synthesis of β-keto esters from dioxinones *via* ketene trapping has been reported: M. Sato, N. Yoneda, N. Katagiri, H. Watanabe and C. Kaneko, *Synthesis*, 1986, 672.

13 M. Sato, Y. Abe and C. Kaneko, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1779.

14 M. Sato, Y. Abe, K. Takayama and C. Kaneko, *J. Heterocycl. Chem.*, 1991, **28**, 241 and references therein.

15 A variety of reactions using dioxinones have been reviewed: C. Kaneko, M. Sato, J. Sakaki and Y. Abe, *J. Heterocycl. Chem.*, 1990, **27**, 25.