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A SHORT, CONVENIENT SYNTHESIS OF 2-ARYLGLYCIDATES *VIA* ARYL-GRIGNARD ADDITION TO AN α-BROMOPYRUVATE

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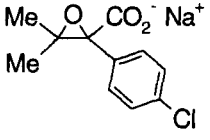
Abstract: A simple procedure has been developed for the preparation of a series of 2-arylglycidates required for herbicidal evaluation. Treatment of the α-bromopyruvate **5** with various aryl Grignard reagents at low temperature gave directly the glycidates **4**. Saponification of these then afforded the desired sodium salts **7**.

A programme to screen random compounds from a wide variety of sources for useful biological properties led to the identification of the glycidate **1**, which produced moderate herbicidal activity.[1]



1

It was hoped that small changes to the structure of **1** might enhance this activity, and thus we embarked on the synthesis of a series of analogues. The

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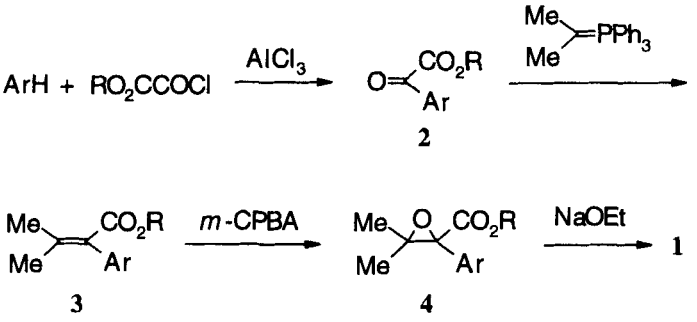
general route which had been used to prepare the original sample of **1** is shown in Scheme 1.[2] The acrylic ester **3** (R = Me), obtained according to the method of Micetich,[3] was converted to the epoxide **4** (R = Me), which was then saponified to give **1**.

Scheme 1

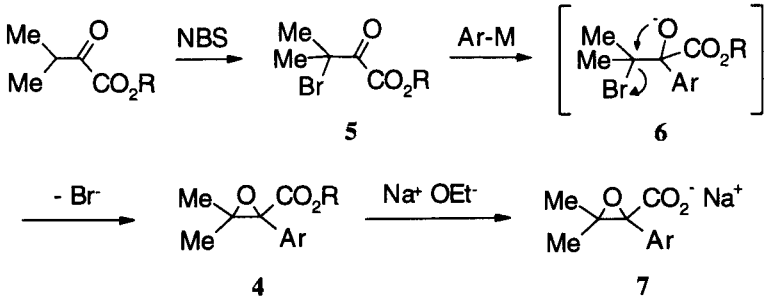


Using this route, several analogues of **1** were prepared and their herbicidal activities were evaluated. It was quickly established that the presence of the two methyl groups at the 3-position of the glycidate is important for the herbicidal activity. Our objective thus became to prepare further analogues which would retain this 3,3-dimethyl substitution, but encompass a wider variety of substituted aryl groups at the 2-position.

The initial route of Scheme 1 is not very suitable for this purpose: Firstly, the Friedel-Crafts step severely restricts the variety of substituted aryl groups which can be introduced into the pyruvates **2** and, secondly, the route is inefficient, since several steps are required for the preparation of each new analogue. An alternative route to the requisite glycidic esters **4** would be the Darzens condensation.[4] However, Zwanenburg reports[2] that only in a few specific cases is it possible to obtain 2-aryl substituted glycidates using the Darzens condensation, and our own attempts to prepare **4** by this method also failed.

A conceptually different approach to **4**, which if successful would provide a much more efficient and flexible procedure for preparing analogues, is depicted in Scheme 2.

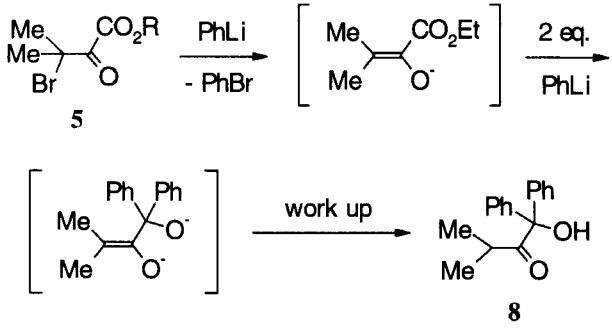
Scheme 2



It was thought that a suitable aryl organometallic reagent could add preferentially to the keto group of **5** to generate intermediate **6**, which should then undergo ring closure with loss of bromide ion to afford the desired glycidate **4**. Although there are literature examples of epoxide formation by the reactions of α-halo-ketones with many different types of organometallic reagents,[5] it appears that such an approach has never been examined for the preparation of 2-alkyl or 2-aryl substituted glycidates. The nearest known transformation of this kind is the reaction of an α-chloropyruvate with ethoxide to give a 2-ethoxy substituted glycidate.[6]

The treatment of ethyl 3-bromo-3-methyl-2-oxobutanoate (**5**, R = Et)[7] with phenyl-lithium in dry THF at -70 °C gave a gross mixture of products in which none of the desired glycidate **4** could be identified. However, when the addition was instead carried out at -100 °C, a small amount (ca. 10%) of **4** was obtained, along with several other products. Careful analysis of the product mixture

revealed the presence of bromobenzene, bi-phenyl, phenol and the alcohol **8**, the formation of which can be rationalised as follows:



5 **8**

Thus, a major side reaction under these conditions involves initial attack of the phenyl-lithium at the bromine atom of **5**, instead of at the carbonyl group as required. This side reaction consumes three equivalents of the organometallic reagent. We concluded that the use of a Grignard reagent in place of the aryl-lithium should favour the addition to the carbonyl group and thus improve the yield of **4**. And indeed, when phenyl-magnesium chloride was used in place of phenyl-lithium, **4** (Ar = Ph, R = Et) was obtained cleanly in 75% isolated yield.

This procedure was then applied to the preparation of a range of glycidates **4**, containing a variety of substituted aryl groups (see Table). The conditions which had been optimised for **4** (Ar = Ph, R = Et) were used without variation for the remaining preparations. In certain cases where lower yields were obtained, we also isolated products in which further aryl Grignard reagent had added to the ester group to produce the corresponding aryl ketone. The esters **4** were saponified to give the ultimate target molecules **7**, the sodium salts, using standard conditions (see Experimental Details).

The following procedure is representative for the preparation of **4**: A solution of ethyl 3-bromo-3-methyl-2-oxobutanoate (**5**, R = Et)[7] (5.6 g, 25 mmol)

Table Examples and Yields of Glycidates **4** and **7**

Example	Ar	**4** (R = Et, %)	**7** (%)
a	Phenyl	75	-
b	3-Chlorophenyl	46	83
c	2-Chlorophenyl	29	68
d	3,5-Dichlorophenyl	30	93
e	2,4-Dichlorophenyl	24	92
f	3,4-Dichlorophenyl	64	80
g	4-Bromophenyl	30	52
h	3,5-Dimethylphenyl	52	67
i	4-Trifluoromethylphenyl	13	80

in dry THF (10 ml) was added dropwise to a stirred solution of phenyl-magnesium chloride (14 ml of a 2.0 M solution in THF, diluted to 50 ml with further THF) under nitrogen at -45 °C. Stirring was continued for ca. 1 h at this temperature and then the solution was allowed to warm gradually over 3 h to room temperature. The reaction mixture was cooled as a mixture of THF (40 ml) and water (10 ml) was added gradually. The crude reaction mixture was extracted with diethyl ether and the organic phase was washed with sodium chloride solution, dried over sodium sulphate and evaporated *in vacuo*. The crude product was purified by flash column chromatography, eluting with a 5:1 mixture of petroleum ether and isopropyl ether, to give **4** (Ar = Ph, R = Et) (4.1 g, 75%) as a colourless oil. T.l.c. and ^{1}H NMR spectroscopy confirmed that the product was pure and identical with an authentic sample, prepared by the original route.

In conclusion, we have developed a short and convenient new synthesis route to 2-aryl substituted glycidates. Using this route, we have successfully prepared a series of analogues which were required for herbicide screening and

which would have been difficult to obtain using the known literature methods. The herbicidal activity of this class of compounds forms the subject of a patent application.[1]

Experimental Details

Preparation of the glycidic esters 4:

Analogues **4b** - **4i** (Table 1 in the text) were prepared by exact analogy with the procedure described in the text for **4a**. In each case, the Grignard reagent was prepared *in situ* from the corresponding aryl chloride (**4b**) or bromide (**4c** - **4i**), by treatment with magnesium in dry THF under nitrogen, prior to the addition of **5** (R = Et). Following flash column chromatography of the crude products, the pure materials were all obtained as colourless oils. Their purities were confirmed by t.l.c. and ^{1}H NMR.

Preparation of the sodium salts 7:

The following procedure is representative for the saponification of **4** to give **7**:
A solution of **4b** (3.0 g, 11.8 mmol) in a mixture of 2.0 N aqueous sodium hydroxide (44.8 ml, 11.2 mmol) and ethanol (50 ml) was refluxed for 16 h. The solution was allowed to cool, filtered through silica and evaporated *in vacuo*. The residue was stirred vigorously with *i*-propanol (100 ml) for 1 h, and then the product was filtered off and dried, giving **7b** (2.3 g, 83%). All of the products were obtained as white, crystalline solids.

^{1}H NMR Data:

All spectra were recorded on a Bruker 300 MHz instrument, using tetramethylsilane (TMS) as internal standard.

4a ($CDCl_3$): δ 7.58 (m, 2H), 7.35 (m, 3H), 4.24 (q, *J* = 7 Hz, 2H), 1.46 (s, 3H), 1.29 (t, *J* = 7 Hz, 3H), 1.06 (s, 3H); **4b** ($CDCl_3$): δ 7.59 (br s, 1H), 7.48 (m, 1H), 7.30 (m, 2H), 4.26 (q, *J* = 7 Hz, 2H), 1.47 (s, 3H), 1.30 (t, *J* = 7 Hz, 3H), 1.07 (s, 3H); **4c** ($CDCl_3$): δ 7.42 (m, 2H), 7.27 (m, 2H), 4.20 (m, 2H), 1.59 (s, 3H), 1.24 (t, *J* = 7 Hz, 3H), 1.18 (s, 3H); **4d** ($CDCl_3$): δ 7.50 (br s, 2H), 7.32 (br s, 1H), 4.28 (q, *J* = 7 Hz, 2H), 1.46 (s, 3H), 1.32 (t, *J* = 7 Hz, 3H), 1.08 (s, 3H); **4e** ($CDCl_3$): δ 7.39 (m, 2H), 7.27 (m, 1H), 4.20 (m, 2H), 1.58 (s, 3H), 1.23 (t, *J* = 7 Hz, 3H), 1.19 (s, 3H); **4f** ($CDCl_3$): δ 7.70 (s, 1H), 7.47 (s, 2H), 4.24 (q, *J* = 7 Hz, 2H), 1.47 (s, 3H), 1.30 (t, *J* = 7 Hz, 3H), 1.07 (s, 3H); **4g** ($CDCl_3$): δ 7.48 (m, 4H), 4.25 (q, *J* = 7 Hz, 2H), 1.47 (s, 3H), 1.28 (t, *J* = 7 Hz, 3H), 1.05 (s, 3H); **4h** ($CDCl_3$): δ 7.19 (br s, 2H), 6.96 (br s, 1H), 4.23 (q, *J* = 7 Hz, 2H), 2.32 (s, 6H), 1.46 (s, 3H), 1.29 (t, *J* = 7 Hz, 3H), 1.08 (s, 3H); **4i** ($CDCl_3$): δ 7.74 (d, *J* = 8 Hz, 2H), 7.63 (d, *J* = 8 Hz, 2H), 4.64 (q, *J* = 7 Hz, 2H), 1.48 (s, 3H), 1.30 (t, *J* = 7 Hz, 3H), 1.04 (s, 3H).

7b (DMSO-d_6): δ 7.69 (br s, 1H), 7.49 (br d, *J* = 7 Hz, 1H), 7.29 (m, 2H), 1.32 (s, 3H), 0.87 (s, 3H); **7c** (DMSO-d_6): δ 7.26 (m, 4H), 1.48 (s, 3H), 1.02 (s, 3H); **7d** (DMSO-d_6): δ 7.58 (s, 2H), 7.44 (s, 1H), 1.34 (s, 3H), 0.90 (s, 3H); **7e** (DMSO-d_6): δ 7.45 (s, 1H), 7.30 (s, 2H), 1.48 (s, 3H), 1.03 (s, 3H); **7f** (DMSO-d_6): δ 7.87 (s, 1H), 7.51 (s, 2H), 1.32 (s, 3H), 0.88 (s, 3H); **7g** (DMSO-d_6): δ 7.53 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8 Hz, 2H), 1.32 (s, 3H), 0.86 (s, 3H); **7h** (DMSO-d_6): δ 7.19 (br s, 2H), 6.81 (br s, 1H), 2.24 (s, 6H), 1.30 (s, 3H), 0.88 (s, 3H); **7i** (DMSO-d_6): δ 7.80 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H), 1.34 (s, 3H), 0.85 (s, 3H).

References and Notes

1. Newton, T. W. and Zwanenburg, B. *European Patent Application* 0641515; A1 (1995).
2. Thijs, L., Smeets, F. L. M., Cillissen, P. J. M., Harmsen, J. and Zwanenburg, B. *Tetrahedron* **1980**, *36*, 2141.

3. (a) Micetich, R. G. *Org. Prep. and Proc.* **1970**, *2*, 249; (b) Raap, R., Chin, C. G. and Micetich, R. G. *Can. J. Chem.* **1971**, *49*, 2143.

4. (a) Newman, M. S. and Magerlein, B. J. *Org. React.* **1949**, *5*, 413; (b) Ballester, M. *Chem. Rev.* **1955**, *55*, 283.

5. Examples include (a) Organo-lithium reagents: Brittain, J. M., Jones, R. A., Sepuldeva-Arques, J. and Aznar-Saliente, T. *Synth. Commun.* **1982**, *12*, 231; (b) Grignard reagents: Greiner, A. *Tetrahedron Lett.* **1989**, *30*, 3547; (c) Organo-tin reagents: Yano, H., Hatta, Y., Baba, A. and Matsuda, H. *Synthesis* **1992**, 693; (d) Organo-zinc reagents: Miginiac, P. and Zamlouty, G. *Bull. Soc. Chim. Fr.* **1975**, 1740.

6. Moraud, B. and Combret, J. C. *C. R. Acad Sci, Ser. C* **1973**, *277*, 523.

7. Seifert, P., Vogel, E., Rossi, A. and Schinz, H. *Helv. Chim. Acta* **1950**, *33*, 725.

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