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Tetrahedron Letters 47 (2006) 1741–1744
Tetrahedron Letters

Is diazomethane addition to chiral α-keto esters subject to substrate diastereocontrol?

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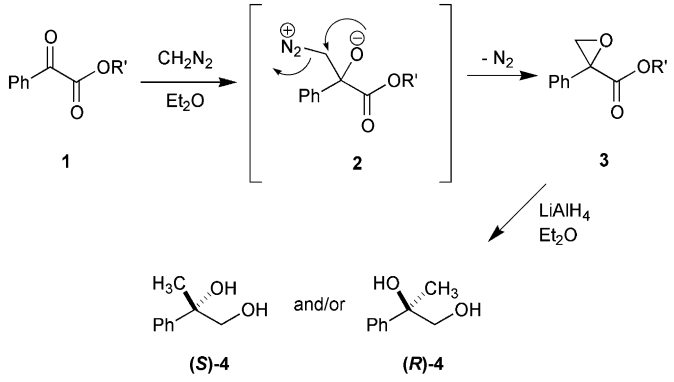
Received 16 November 2005; revised 13 December 2005; accepted 14 December 2005
Available online 26 January 2006

Abstract—The uncatalyzed reaction of diazomethane with chiral benzoylformate esters results in the formation of α-oxiranyl esters without significant facial discrimination in almost every case.

Diazomethane is recognized to be capable of reaction with vicinal polyketones at the more electron-deficient carbonyl site with methylene transfer to give α-epoxy ketones.[1] Although this process holds utility because it assembles oxiranes via late-stage installation of the methylene carbon, it has traditionally suffered limited scope until recently.[2] Reports documenting the related transformation of α-keto esters typified by **1** to their glycidic counterparts (e.g., **3**) are yet more sparse.[3] The merits of the **1**→**3** conversion reside in the dense functionality that is generated, thereby providing handles for further chemical manipulation. Of added potential benefit is the fact that the prochiral reaction site in **1** becomes a stereogenic center in the cycloadduct. Consequently, if this transformation could be made suitably diastereoselective, its synthetic value would be significantly enhanced.

In our first attempts in this direction, the esterification of terpene-derived alcohols with benzoylformyl chloride[4] was carried out. It was not clear which face of the ketone carbonyl would be attacked preferentially if recognizably biased (see **2**). The provisions that were made to ultimately determine the absolute configuration of the oxiranyl methine center involved the lithium aluminum hydride reduction of individual samples of **3** to diol **4**. This step results in removal of the chiral auxiliary and conversion to a product whose three-dimensional structure and optical rotation have been well defined by others.[5]



Keywords: [2+1]Cycloadditions; Glycidic esters; Benzoylformate esters; Diastereoselective methylene transfer; Asymmetric induction.
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0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.12.137

When ester **5**, made available by the initial reduction of (+)-nopinone with $NaBH_4$,[6] was treated with ethereal diazomethane under our optimized conditions (expt. 1), no asymmetric induction transpired during formation of the oxirane ring (Table 1). The substrate into which (1*S*,2*R*,4*S*)-7,7-dimethyl-1-vinyl-2-norbornanol[7] (expt. 4) and (−)-menthol (expt. 5) had been incorporated likewise afforded glycidic esters having equal levels of the two possible diastereomers (^{1}H NMR analysis).[8] The situation was moderately improved when the esters derived from (−)-3-isothujanol[9] (expt. 2) and commercial (−)-*trans*-myrtanol (expt. 3) were similarly treated. While this pair of experiments gave essentially identical 52:48 distributions of α-epoxy esters, the major diol **4** in the first instance involving **6** proved to be *S*-configured and antipodal to that observed from **7**. When the series was extended to include (−)-8-phenylmenthol,[10] its benzoylformate ester **10** exhibited enhanced discrimination, leading ultimately to (*S*)-**4** with a dr of 2.5:1 (expt. 6).

Since modest asymmetric induction occurs in the course of this methylene transfer, we were prompted to evaluate the possible positive impact to be gained by steric hindrance as well as π-stacking[11] involving properly positioned substituents offering different levels of through–space interaction (Table 2). If the selectivity arises from outside approach of CH_2N_2 to the *Re* face of the ketone carbonyl in the conformation defined by **A** (Scheme 1), the possibility exists that an increase in the overall size of R (e.g., *tert*-butyl) or a lengthening of the tether to the aryl groups in R (e.g., **12**–**15**) might suitably enhance the level of asymmetric induction. Alternatively, the same structural changes could foster enhanced *Si* attack via the more extended conformer **B**. The camphor-based building block was selected because of its conformational rigidity and the dual *exo* projection of its two C–O bonds. As matters turned out, esters **11**–**15** exhibited a uniform preference for generating more of that α-epoxy ester serving as precursor to the *S*-enantiomeric diol **4**. The dr values ranged from a low of 1.1:1 for **13** to a high of 2:1 for **15**. Clearly, steric and electronic factors do not constitute a convenient tool for achieving high-level diastereocontrol in these systems.

Table 1. Reaction of benzoylformate esters derived from terpenic alcohols with diazomethane

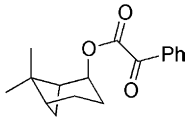
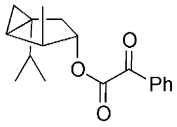
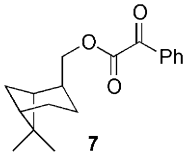
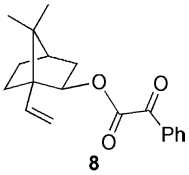
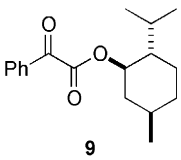
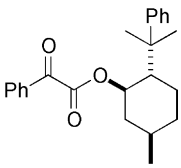
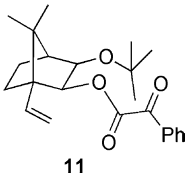
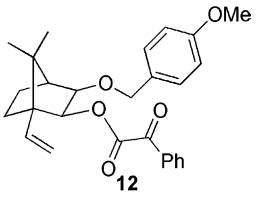
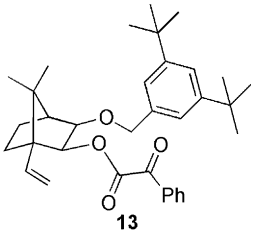
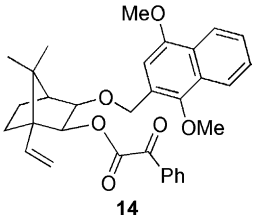
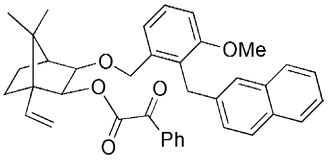
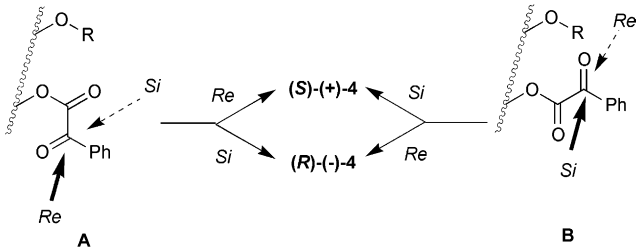
Expt.	Substrate	% Conversion	dr	Diol configuration
1	 **5**	100	1:1	—-
2	 **6**	100	1.1:1	*S*
3	 **7**	100	1.1:1	*R*
4	 **8**	70	1:1	—-
5	 **9**	100	1:1	—-
6	 **10**	**100**	**2.5:1**	***S***

Table 2. Response of benzoylformate esters derived from hindered/arylated carbinols to reaction with diazomethane

Expt.	Substrate	% Conversion	dr	Diol configuration
7	 **11**	90	1.5:1	*S*
8	 **12**	85	1.2:1	*S*
9	 **13**	100	1.1:1	*S*
10	 **14**	75	1.2:1	*S*
11	 **15**	**100**	**2:1**	***S***



Scheme 1. Diazomethane approach to benzoylformate esters involving two conformers having opposed carbonyl dipoles.

Through this study, we have demonstrated that it is difficult to realize significant substrate control when diazomethane is involved as the co-reactant in α-epoxy ester generation. While the level to which the methylenated product is formed is very high, derivatization with a sterically bulky or aryl-rich alcohol component is not conducive to enhancing the dr beyond the 2.5:1 level. However, while product ratios of this magnitude are not considered to be selective by most definitions, the present protocol is simple enough and the glycidic ester isomers are readily isolable in most cases.[12] Such an outcome may prove to be an acceptable alternative over other options.

References and notes

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8. The oxiranyl ring protons of the glycidic esters exhibit widely spaced chemical shifts ($CDCl_3$, 400 MHz): expt. 1—δ 2.88/3.35; expt. 2—δ 2.95/3.42; expt. 3—δ 2.16/3.32; expt. 4—δ 2.84/3.29; expt. 5—δ 2.95/3.38; expt. 6—δ 2.66/3.00.
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12. General procedure: the α-keto ester (1 equiv) was dissolved in anhydrous Et_2O (0.1 M). A freshly prepared solution of CH_2N_2 (10 equiv) was added in one portion. Stirring was maintained for 8–12 h, and % conversion was monitored by TLC (10% EtOAc/Hex). When necessary, additional CH_2N_2 was added every 8–12 h for up to 3 days. Upon completion of reaction, the solvent was removed in vacuo. The dr was determined by ^1H NMR analysis of the unpurified mixture. The diastereomeric epoxides could also be separated by flash chromatography on silica gel (5–10% Et_2O/hexanes) for the epoxides derived from **10**.