HOMOLOGATION OF VICINAL POLYKETONE NETWORKS TO EPOXY KETONES WITH DIAZOMETHANE[†]

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Abstract – Admixture of vicinal di-, tri-, and tetraketones with ethereal diazomethane results in one-time methylene transfer to the less hindered face of the sterically most accessible and electron-deficient carbonyl group to deliver epoxy ketones in a highly selective manner unless ring strain effects contravene.

The epoxy ketone functional group is valued in organic synthesis because of the several reactive sites resident therein. Despite the breadth of chemical transformations to which this compound class has been subjected, their preparation has relied almost exclusively on the alkaline peroxidation of α,β-unsaturated ketones.[1,2] The oxygen atom of the oxirane ring is consequently introduced last. Occasions can be envisioned where insertion of the carbon atom in the final maneuver is desirable for stereochemical reasons or because the particular conjugated enone is notably prone to anionic polymerization.

Rather remarkably, the possibility of adding diazomethane to vicinal polycarbonyl functional groups has been only infrequently applied. Beyond this, the few early reports of the implementation of this reaction are hardly indicative of its latent synthetic potential or breadth.[3] As well, reports documenting the transformation of α-keto esters such as **1** into **2** are limited.[4] For α-dicarbonyl systems recognized to have an elevated enol content, *O*-methylated vinylogous esters typified by **4** are formed under similar conditions.[5]
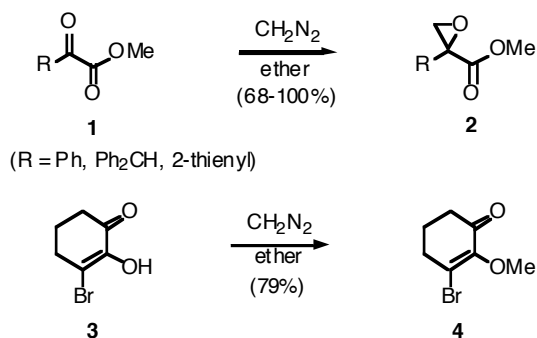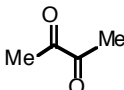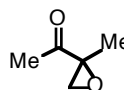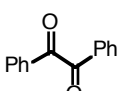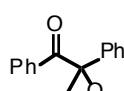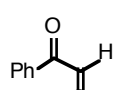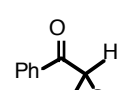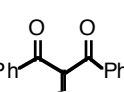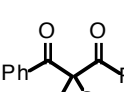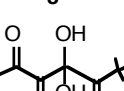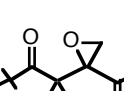
We now report on the general feasibility of adding diazomethane to vicinal polyketones R(CO)$_n$R' where n = 2-4, which reaction often results in one-time insertion of an oxiranyl carbon. A priori, the regioselectivity and π-facial stereoselectivity of this process can be expected to be controlled by steric factors and extendable to cyclic and open-chain substrates alike.

First to be explored were the acyclic systems (**5-9**) (Table I). In all five examples, the reactant was treated with approximately 10 equiv of ethereal diazomethane and allowed to stir overnight at room temperature. The co-addition of silica gel to the reaction mixture as in the case of **8** served to accelerate the conversion to product and enhance the yield of oxirane to some degree. As expected, the homologation of **7** was totally regioselective, with exclusive involvement of its aldehyde carbonyl.
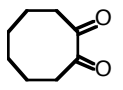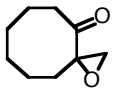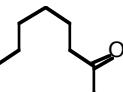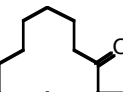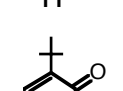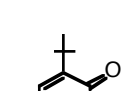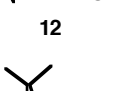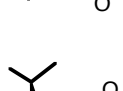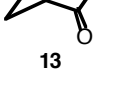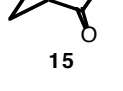
The five cyclic α-diketones (**10-14**) selected for study (Table II) are all recognized to bypass measurable equilibration with their diosphenol tautomer. For **12** and **14**, no prototropic shift is possible. In the first three examples, reaction proceeded smoothly to generate the anticipated epoxy ketones in good yield. The regiochemistry exhibited by **12** is clearly a consequence of prevailing steric shielding, as is the

Table I. Acyclic systems[a]

reactant	product	yield, %
5		54
6		87
7		40
8		80[b]
9		81[c]

[a] 10 equiv. of CH$_2$N$_2$ in ether. [b] SiO$_2$ also present. [c] ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.20 (s, 4 H), 1.24 (s, 18 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 215.3, 74.0. 64.3, 42.8, 26.5.

Table II. Cyclic systems[a]

reactant	product	yield, %
10		53
11		69
12		77[b]
13	**15**	92[b,c]
14	**16** + **17** (73 : 27)	84[c]

[a] 10 equiv. of CH$_2$N$_2$ in ether. [b] SiO$_2$ also present. [c] Based on recovered starting material (for **13**, 10% conversion to **15**; for **14**, 55% conversion to **16/17**).

response of **13**. Where **13** and **14** are concerned, the capture of CH_2N_2 is kinetically retarded because of the space demands enforced by their bicyclic architecture. For this reason, the yields of **15-17** should not be regarded as optimized under the generic conditions adopted herein. Beyond this, the experiment involving **14** demonstrates that the strain inherent in camphorquinone is such as to deter advancement of **18** to the epoxide. Instead, ring expansion to **19** operates, with subsequent *O*-methylation of both possible tautomers.[6]
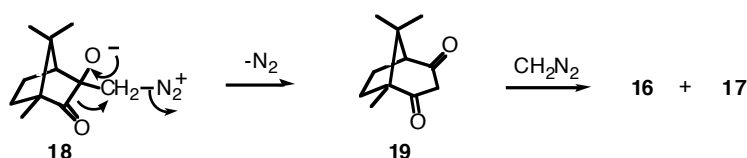
The aryl-fused reactants (**20-22**) follow the established pattern of behavior, although conversion to product occurs more sluggishly and with increased opportunity for unwanted side reactions (Table III). The regioselectivity exhibited by **21** conforms to that observed in its reaction with other nucleophilic species.[7]

To understand better the scope of this reaction, we turned finally to the 1,2-cyclobutenedione class of reactants (Table IV). Although dimethyl squarate (**25**) proved to give relatively messy results, all three members of the **23-25** subset were transformed into the corresponding cyclopentene-1,3-diones. Like **14**, therefore, ring strain issues did not allow for epoxide formation. However, unlike **14**, the diketonic products did not react further with diazomethane, a result attributable to vanishing levels of enol content so as to avoid the development of destabilizing cyclopentadienone characteristics.

Table III. Aryl-fused α-diketones[a]

reactant	product	yield, %
20		88[b,c]
21		96[b,c]
22		53[c]

[a-c] See footnotes to Table II.

Table IV. Cyclobutene-1,2-diones[a]

reactant	product	yield, %
23		58[b,c]
24		69[b]
25		28[b,d]

[a, b] See footnotes to Table II. [c] Herndon, J. W.; Patel, P. P. *Tetrahedron Lett.* **1997**, *38*, 59.
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In summary, CH_2N_2 has been shown to react readily with vicinal polyketones. The initial attack is followed by denitrogenation with ring closure to give an oxirane unless ring strain effects are present. Under the latter circumstances, ring expansion results to deliver cyclic 1,3-diketones. The latter may react with a second equivalent of diazomethane depending on structural features.

ACKNOWLEDGMENT

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