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AN EFFICIENT AND HIGHLY FLEXIBLE SYNTHESIS OF α,β-UNSATURATED γ-OXOESTERS

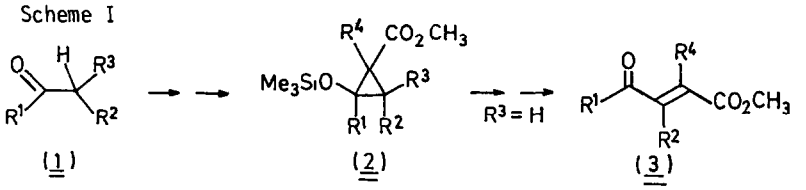
Ingrid Bohm, Rick Schulz and Hans-Ulrich Reissig*

Institut fur Organische Chemie der Universitat,
Am Hubland, D-8700 Wurzburg, Germany

Summary Siloxy substituted methyl cyclopropanecarboxylates are cleaved by bromine to afford α-bromo-γ-oxoester and, after treatment with triethylamine, good yields of α,β-unsaturated γ-oxoesters

Many macrolide antibiotics incorporate the γ-oxocrotonate block [1-3]. In addition, the more general type of α,β-unsaturated γ-oxoester 3 can serve as an acceptor towards nucleophiles or as a potent dienophile in Diels-Alder reactions [4] Although a number of methods [5] exist for the preparation of this structural unit there are many restrictions concerning the substituents R^1, R^2 and R^4 as well as the mildness of reaction conditions, simplicity, and the availability of starting materials We here want to report on the conversion of siloxy substituted methyl cyclopropanecarboxylates (2) to methyl α,β-unsaturated γ-oxocarboxylates (3), which constitutes an overall α-methoxycarbonylmethylenation of a carbonyl compound (1) (scheme I)

Scheme I

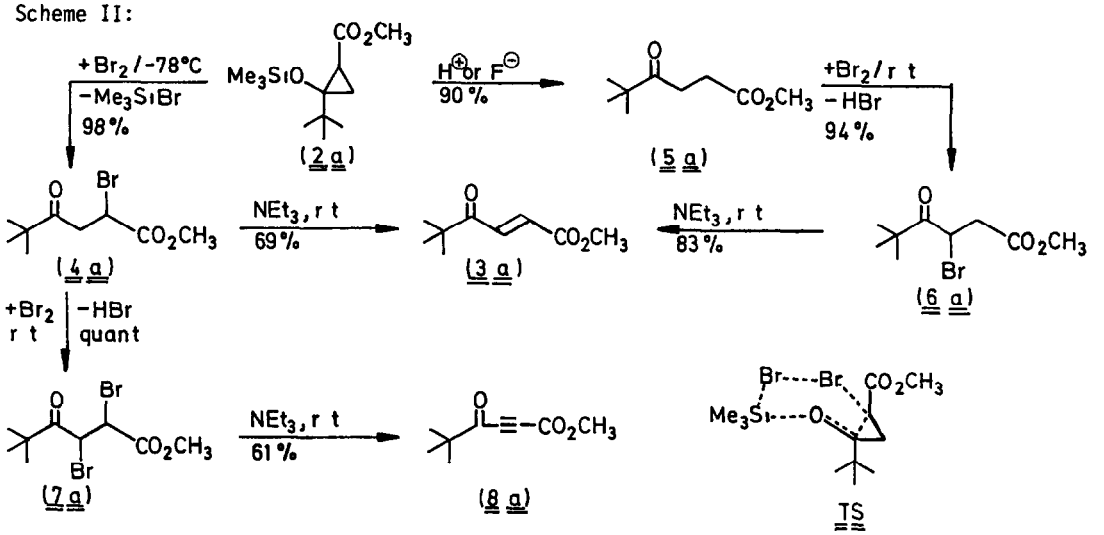


(1) (2) (3)

The cyclopropanes (2) are easily synthesized from trimethylsilyl enolethers - corresponding to the carbonyl compound (1) - and methyl diazoacetate in good yields [6] Regarding R^4 they can be widely varied via deprotonation and alkylation [7] These donor-acceptor activated cyclopropanes (2) undergo smooth ring opening with a variety of electrophiles [8]

Cyclopropane (2a) readily reacts with one equivalent of bromine at -78°C to provide the α-bromo-γ-oxoester (4a) quantitatively, and trimethylsilyl bromide (scheme II). (4a) can spectroscopically be distinguished from its isomer, the β-bromo-γ-oxoester (6a) obtained by ring opening [6] of (2a) with $NEt_3 \cdot 2HF$ or aqueous acid giving (5a) and subsequent bromination of the latter at room temperature

Scheme II:



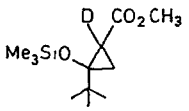
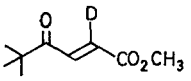
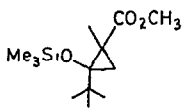
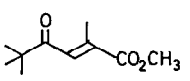
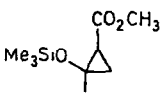
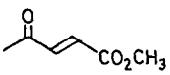
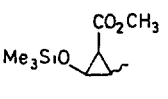
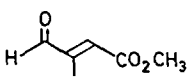
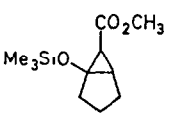
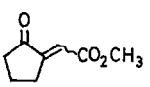
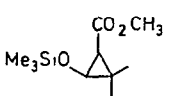
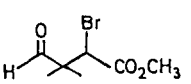
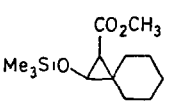
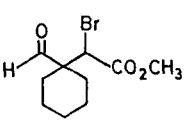
As in all reactions investigated so far that cyclopropane bond is cleaved which is activated by the vicinal location of the donor and the acceptor substituent [8] Similar introduction of bromine or other electrophiles in β-position to the newly created carbonyl group was observed for simpler cyclopropanol derivatives [9,10]. The regiochemistry may best be rationalized by a transition state similar to TS; however, a stepwise process cannot be excluded - an autocatalytic effect of trimethylsilyl bromide (lewis acid!) is also possible.

After treatment with triethylamine, both bromo esters (4a) and (6a) give the methyl γ-oxocrotonate (3a) [5f] in good yield. For (3a) and (3d) (see table) where $R^2 = R^4 = H$ the E-configuration of the olefin is established by the coupling constants of J = 15 and 16 Hz respectively in the ^{1}H-NMR spectra.

Interestingly, by addition of 2 equivalents of bromine to (2a) rapid decolorisation is observed at room temperature Evaporation leads to a quantitative yield of the α,β-dibromo-γ-oxoester (7a) (scheme II). Obviously the intermediate (4a) is brominated a second time, now α to the keto function. Action of triethylamine on (7a) affords the methyl β-pivaloyl propiolate (8a). Thus, using very simple reagents the siloxy substituted cyclopropane serves as precursor for γ-oxoester with a single, a double or a triple bond between C-α and C-β (see (5a), (3a) and (8a) in scheme II).

Table 1 shows our results with cyclopropanes (2b) to (2h). Whereas (3b) and (3c) are obtained by the two step process described for (3a) (method A), (4d) - (4f) seem to be quite unstable However, in situ treatment at -78°C with triethylamine and subsequent warm up to room temperature is a suitable one pot procedure (method B) providing (3d) - (3f) (2g) and (2h) and bromine deliver (4g) and (4h) isolated after distillation in good yields (method C) Due to their polyfunctionality these α-bromoesters [11] might be versatile starting materials for further reactions.

Table: Synthesized α,β-unsaturated γ-Oxoester and α-Bromo-γ-oxoester

educt	method [a]	product	yield [b]	boiling point [c] (°C/mm)
 (2b)	A	 (3b)	76 %	120 - 130/16
 (2c)	A	 (3c)	67 %	50 - 55/0.05
 (2d)	B	 (3d)	72 %	m p. 58 - 59°C (Lit 5b 60 5°C)
 (2e)	B	 (3e)	61 %	75 - 80/17 (Lit 5a. 56 - 57/7)
 (2f)	B	 (3f)	74 %	60 - 70/0 03 m p. 35 - 37°C (Lit 5d: 38°C)
 (2g)	C	 (3g)	82 %	145 - 150/15
 (2h)	C	 (3h)	85 %	90 - 105/0 01

[a] A 1 1 5 eq Br_2 in CH_2Cl_2 or CH_2Cl_2/CCl_4, 10 min -78°C, 2 3 eq $Na_2S_2O_3$ -78°C → r t , filtration, evaporation, 3 4 eq NEt_3, aqueous work up, distillation. B 1 like A, 2. 4 eq NEt_3 -78°C → r t , aqueous work up, distillation C: 1 and 2. like A, 3 distillation.

[b] Non-optimized yields of isolated products after Kugelrohr distillation, all compounds gave appropiate spectra, new products deliver satisfactory combustion analyses

[c] Bath temperature.

In summary, action of bromine on the donor-acceptor-substituted cyclopropanes (2) afford compounds which are well suited for many purposes in organic synthesis, thus widening the synthetic scope of this type of cyclopropanes [12]

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