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A NEW CHIRAL ALKYLATION METHODOLOGY FOR THE SYNTHESIS OF 2-ALKYL-4-KETOACIDS IN HIGH OPTICAL PURITY USING 2-TRIFLYLOXY ESTERS

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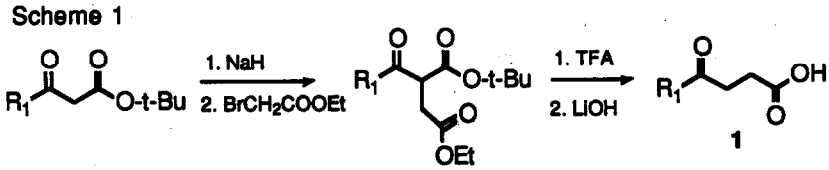
Summary: Optically active 2-triflyloxy esters are excellent alkylating agents for β-ketoester enolates. Decarboxylation of the alkylation products gives 2-substituted-4-ketoacid derivatives in high optical purities.

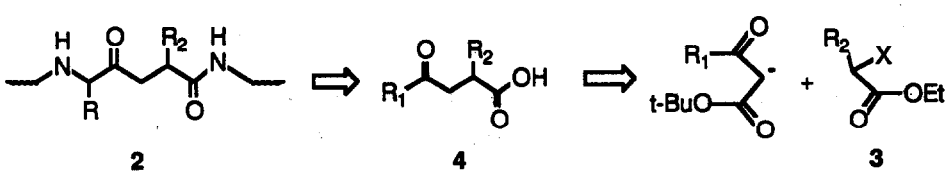
We recently reported a new method for the synthesis of ketomethylene peptide isosteres in which the C-2 to C-3 carbon-carbon bond of the key γ-ketoacid segment **1** is formed by the reaction of a 3-ketoester enolate with ethyl bromoacetate (Scheme 1).[1]

Scheme 1



One limitation of this approach is that ethyl bromoacetate gives a γ-ketoester product which is unsubstituted at C-2. Since many interesting ketomethylene peptide isosteres have alkyl substituents at C-2 (eg. **2**), a useful extension of the strategy would allow for the incorporation of substituents at C-2 of the γ-ketoacid unit (eg. **4**)with control of the stereochemistry at that position. To do this requires that 2-substituted esters other than bromoacetate (eg. **3**) be used as the alkylating agent.

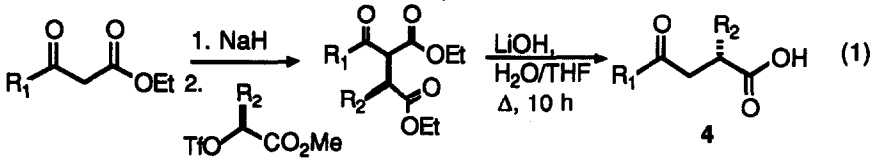
Scheme 2



However, reports of 2-haloesters other than ethyl bromoacetate being used successfully as alkylating agents are very scarce.[2] Apparently the reactivity of 2-haloesters (**3**, X= Br, I) towards nucleophiles is attenuated significantly by R_2 groups other than hydrogen, to the extent that only very low yields of alkylation products can

be obtained. Previous studies of the reactions of 2-sulfonyloxy esters with nucleophiles did not include any carbon centered nucleophiles,[3] however, the excellent results obtained with a variety of nucleophile types suggested that 2-triflyloxy esters (3, X= OTf) might be excellent alkylating agents for β-ketoester enolates. In the first place they are very effective alkylating agents towards a variety of nucleophiles that fail to react with 2-bromoesters.[3b,f] In the second place they can be easily prepared with high optical purity[4] so that they could potentially lead to stereochemical control at C-2 of the 4-ketoacid product 4. We are pleased to report that 2-triflyloxy esters are excellent alkylating agents for β-ketoester enolates and the resulting 2-substituted 4-ketoacid products are produced in good yields and high optical purities. This utilization of 2-triflyloxyesters as carbon alkylating agents thus provides an excellent method for the synthesis of 2-substituted ketomethylene peptide isosteres.

Ethyl 3-ketoesters (Method A) **5a-d** were chosen initially because they could be hydrolyzed using lithium hydroxide, a method used previously for the hydrolysis of amino acid esters without detectable racemizatiion.[4a] The 3-ketoester **5** was converted to its enolate in THF, treated with a dichloromethane solution of a 2-triflyloxy



(1)

5a, R_1=Me **6a**, R_2=Me
b, R_1=Et **b**, R_2=i-Bu
c, R_1=n-Pr **c**, R_2=CH_2Ph
d, R_1=i-Pr **d**, R_2=Ph
e, R_1=Ph

Table 1. Synthesis of 2-Substituted-4-ketoalkanoic Acids **4** from the Reaction of Ethyl 3-Ketoesters **5** with 2-Triflyloxy Esters **6** (Method A).

Entry	Reactants		Product	Yield (%)	de (%)[a]	S:R[b]
1.	**5a**	**6a**	**4aa**	64	94	97:3
2.	**5a**	**6b**	**4ab**	58	68	84:16
3.	**5a**	**6c**	**4ac**	76	71	86:14
4.	**5a**	**6d**	**4ad**	85	0	50:50
5.	**5b**	**6a**	**4ba**	65	92	94:4
6.	**5b**	**6c**	**4bc**	56	66	83:17
7.	**5c**	**6a**	**4ca**	90	68	84:16
8.	**5d**	**6a**	**4da**	84	52	76:24
9.	**5d**	**6c**	**4dc**	62	28	64:36
10.	**5e**	**6a**	**4ea**	44	94[c]	97:3

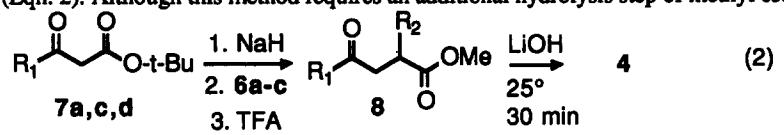
a. Diastereomeric excess determined from the coupling of acid **4** with (S)-(-)-a-methyl-benzylamine. b. Ratio of S:R enantiomers of acid **4**. c. Optical purity determined by coupling with Pro-OMe.

ester **6a-d**, and stirred at room temperature overnight. The crude product was refluxed with lithium hydroxide in aqueous THF for 10 h to give the 4-keto acids **4** in good yields (Eqn. 1). While hydrolysis takes place relatively rapidly (30-60 min), the long reflux period was necessary for complete decarboxylation of the β-ketocarboxylate anion formed by basic hydrolysis. The optical purity of the 2-alkyl-4-ketoacid products **4** was determined by coupling the ketoacid with optically pure α-methylbenzylamine to give α-methylbenzylamides and measuring the ratio of diastereomers by hplc and/or ^{1}H nmr (Table 1).

The absolute configuration of **4ea** is S since its optical rotation $[\alpha]_D$ -35° (c 1.0, EtOH) is similar to that of a partially resolved sample $[\alpha]_D$ -31° (c 1.0, EtOH) whose configuration was shown to be S by X-ray analysis of its proline derivative.[5] Thus alkylation of ketoester **5e** with triflyloxy ester **6a** occurs with inversion of configuration, which is also assumed operative for the other alkylations reported here. Net inversion of configuration is consistent with direct C-alkylation of the ambident enolate nucleophile by the triflyloxy ester.

The results in Table 1 show that good optical purities are obtained in most cases.[6] It was found that significant racemization takes place during the reflux period with lithium hydroxide, which is needed to effect decarboxylation.[7,8] This was demonstrated by carrying out hydrolysis of the crude alkylation product from the reaction of **5a** and **6b** with LiOH at room temperature for 1 h. After neutralization to pH 6, the hydrolyzed products were extracted into benzene and refluxed for 2 h, whereupon smooth decarboxylation occurred to give **4ab** (57%) with a much improved S:R ratio of 93 : 7 (cf, Entry 2, Table 1). Obviously decarboxylation carried out under neutral conditions gives much less racemization.

Based on these results *tert*-butyl esters (Method B) **7a,c,d** were used as the enolate nucleophile because acidic conditions could be used for deesterification and decarboxylation.[1,9] Esters **7a,c,d** were converted to their enolates and treated with 2-triflyloxy esters **6a-c**. The crude alkylation products were deesterified and decarboxylated by stirring with TFA for 24 h. The resulting γ-ketoesters **8** were saponified to γ-ketoacids with LiOH (Eqn. 2). Although this method requires an additional hydrolysis step of methyl ester **8** to produce the 4-



(2)

Table 2. Synthesis of 2-Substituted-4-ketoalkanoic Acids **4** from the Reaction of t-Butyl 3-Ketoesters **7** with 2-Triflyloxy Esters **6** (Method B).

Entry	Reagents		Product	Yield (%)	de(%)[a]	S:R[b]
1.	**7a**	**6a**	**4aa**	54	98	99:1
2.	**7a**	**6b**	**4ab**	54	88	94:6
3.	**7a**	**6c**	**4ac**	53	80	90:10
4.	**7c**	**6a**	**4ca**	61	93[c]	96:4
5.	**7d**	**6c**	**4dc**	72	76[c]	88:12

a. Diastereomeric excess determined from the coupling of acid **4** with (S)-(-)-α-methylbenzylamine. b. Ratio of S:R enantiomers of acid **4**. c. Hydrolysis and decarboxylation: TFA / RT, 30 min, neutralization to pH6, and benzene reflux, 2h.

ketoacid **4**, the data collected in Table 2 show that good yields are still obtained, and the optical purities are quite high. The reaction time can be shortened considerably by deesterification with TFA (30 min), neutralization to pH 6, and refluxing in benzene 2 h. Identical results were obtained for **4ab** with this shortened procedure as for the longer, room temperature procedure reported in Table 2, Entry 2, and excellent results were obtained for **4ca** and **4dc** using the shorter procedure (Entry 4,5).

The chiral alkylation methodology described above for the preparation of 2-alkylated-4-ketoesters and acids is noteworthy in several respects. To the best of our knowledge it is the first general method for the formation of carbon-carbon bonds to the α-position of esters by a substitution process. Second 2-alkyl-4-ketoacids are produced in acceptable yields and high optical purities, and are themselves important synthetic intermediates.[10] Finally 2-alkylated-4-ketoacids with chiral α-alkyl substituents can be easily converted to ketomethylene peptide isosteres using existing methodology,[1] thus this alkylation strategy is very useful for the synthesis of a variety of potentially important protease inhibitors. Extensions of this methodology are under active investigation.

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