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LETTERS

AN INDIUM-PROMOTED ALTERNATIVE TO THE KNOEVENAGEL CONDENSATION OF ALDEHYDES WITH METHYL ACETOACETATE

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Abstract: Addition of methyl (*E*)-4-bromo-3-methoxycrotonate to aldehydes in the presence of indium and water delivers β-hydroxy esters, acidic hydrolysis of which leads to Knoevenagel-like adducts.

Keywords: *indium, allylation, keto esters, Knoevenagel reaction, reactions in water*

As a general reaction type, Knoevenagel condensations constitute a rather versatile class of carbon-carbon bond-forming processes with many obvious applications in organic synthesis. Over the past several years, several investigations have been reported that demonstrate the utility of the basic reaction in solid phase synthesis[1] and in the elaboration of natural products.[2] Microwave enhancement[3] and other forms of catalysis[4] have also recently been probed.

Major restrictions to the broad application of the Knoevenagel reaction involve the inability to arrest the coupling of *aliphatic* aldehydes with cyclic 1,3-diketones[5] and β-keto esters[6] at the monoaddition stage. This complication stems from the fact that the initial products **1** and **2** are highly reactive Michael acceptors capable of engaging the unreacted dicarbonyl reagent in rapid 1,4-addition to give bis-adducts. In 1994, Fuchs and Paquette described a general procedure for intercepting **1** with thiophenol, thereby allowing for regeneration of the enedione under conditions more suited to its kinetic stability.[7]

Detailed herein is an entirely different and very simple approach that permits ready access to the broad category of compounds defined by **2**. The strategy is based on the recognition that the entire β-keto ester subunit of **2** can be nucleophilically linked to an aldehyde in masked form *under aqueous conditions* through utilization of indium metal.[8,9] Submission of the allylation product obtained in this manner to tandem acid hydrolysis and dehydration delivers **2** efficiently.

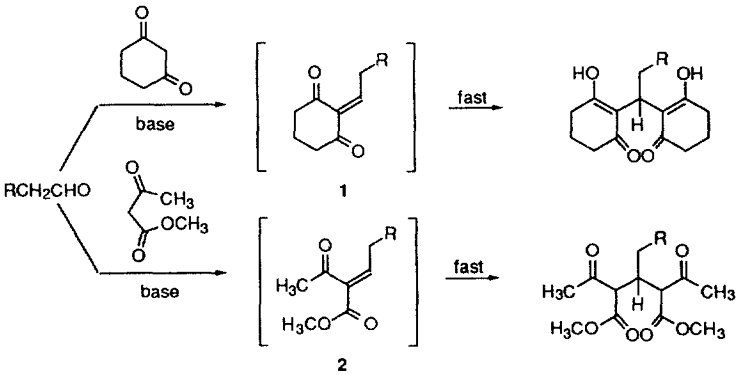

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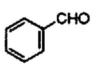
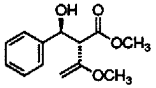
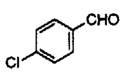
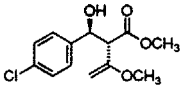
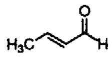
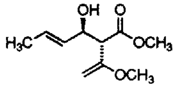
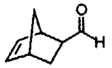
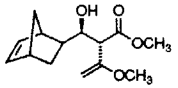
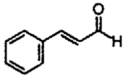
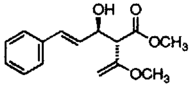
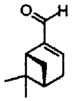
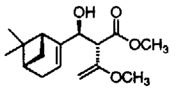
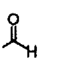
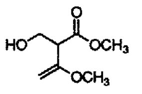
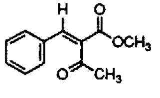
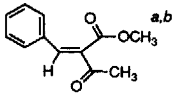
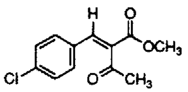
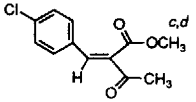
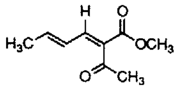
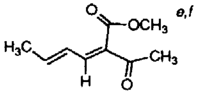
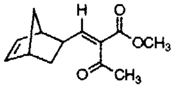
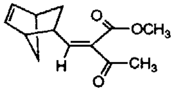
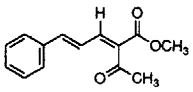
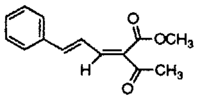
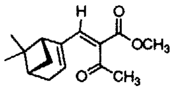
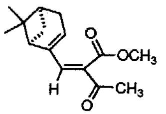
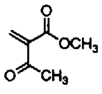
Table 1. Indium-Promoted Condensations of 3 with Various Aldehydes and Acid Hydrolysis of the Carbinols.

expt	aldehyde	major adduct	anti/syn ratio	% yield
1		 **4**	8:1	85
2		 **5**	9.7:1	88
3		 **6**	13:1	63
4		 **7**	1.4:1	74
5		 **8**	16.5:1	82
6		 **9**	1:1.5	58
7		 **10**	---	69

expt	carbinol	products		E/Z ratio	% yield
8	**4**	 **11**	 **12**	1:2.2	83
9	**5**	 **13**	 **14**	1:1.2	83
10	**6**	 **15**	 **16**	1:1	76
11	**7**	 **17**	 **18**	1:1.3	73
12	**8**	 **19**	 **20**	1:2.4	79
13	**9**	 **21**	 **22**	2.9:1	71
14	**10**	 **23**		---	0

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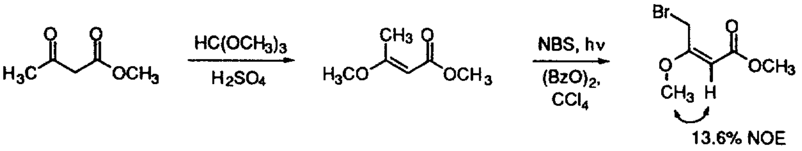
A salient feature of the new approach to **2** is that C-C bond formation occurs in aqueous tetrahydrofuran by way of an allylindium intermediate. As is customary for these processes,[10] the adoption of a Felkin-Ahn transition state was anticipated.

Bromide **3** was prepared by *O*-methylation of methyl acetoacetate and subsequent exposure to *N*-bromosuccinimide in a conventional way.[11] The lone isomer that results was shown to possess the *E* configuration on the basis of an NOE analysis.



3

In an effort to circumvent possible complication from aldehydes having limited solubility in water, all allylations were carried out in a 4:1 mixture of saturated NH_4Cl solution and THF. At a concentration of 2 mL per mmol of aldehyde and with 1.5 equiv of indium powder under conditions of vigorous agitation for 48 h, condensation proceeded quite satisfactorily with a variety of aldehydes (Table 1). No yield is considered to be optimized. In all cases, the progress of reaction was evidenced by formation of a white chalky residue.

Benzaldehyde was found to undergo smooth conversion to an 8:1 diastereomeric mixture of β-hydroxy esters (300 MHz ^1H NMR integration). This initial case study proved to be exemplary. When 4-chlorobenzaldehyde was the reaction partner to **3**, a comparable yield (86%) of two products was again realized. In this instance, the dominant component (9.7:1) proved to be crystalline, thereby permitting the unequivocal assignment of anti stereochemistry as in **5** (Figure 1).

Armed with this information, we found it possible to distinguish between the other 2,3-anti and 2,3-syn diastereomers by means of ^1H NMR correlation. In all of the cases examined here, the anti adduct exhibits a wider chemical shift gap between its carbinol proton and the allylic hydrogen residing α to the carbomethoxy group relative to the syn counterpart (Table 2).

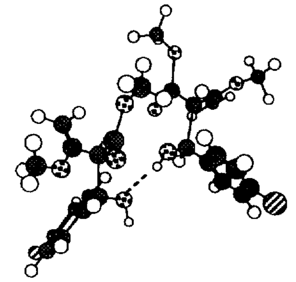


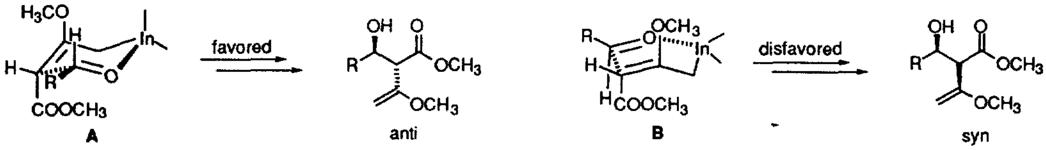
Figure 1. ORTEP diagram of **5**.

Table 2. Diagnostic Chemical Shifts for the Anti (4-9) and Syn β-Hydroxy Esters (300 MHz, $CDCl_3$).

compd	proton chemical shifts, δ	Δδ	compd	proton chemical shifts, δ	Δδ
4	5.18, 3.43	1.75	**7**	6.10, 3.11	2.99
syn	5.03, 3.58	1.45	syn	5.96, 3.22	2.74
5	5.14, 3.33	1.81	**8**	4.81, 3.29	1.52
syn	4.92, 3.44	1.48	syn	4.57, 3.38	1.19
6	4.52, 3.15	1.37	**9**	5.53, 4.48	1.05
syn	4.31, 3.26	1.05	syn	5.12, 4.53	0.59

When α,β-unsaturated aldehydes typified by crotonaldehyde and cinnamaldehyde were examined, somewhat more elevated anti/syn ratios were noted. In contrast, attachment of the CHO functionality directly to a bicyclic framework as in *exo*-5-norbornene-2-carboxaldehyde or (-)-myrtenal was met with a near-normalization of the anti/syn ratio. This enhanced level of syn diastereomer production has no apparent relationship to the presence of a double bond in conjugation with the carbonyl group.

The very respectable stereoselectivity observed in the acyclic examples necessarily implicates preferred adoption of transition state **A** relative to **B**. Thus, the significant bias for anti β-hydroxy ester formation observed in several examples suggests the involvement of a chair-like transition state in which coordination of the indium to the carbonyl oxygen activates the aldehyde for nucleophilic attack, while providing the necessary framework for transmission of stereochemical information. The more equitable anti/syn product distribution noted in runs 4 and 6 when bicycloalkyl moieties constitute an integral part of the R group reveals that the nonbonded steric interactions operative in **A** and **B** can be brought into closer balance under these circumstances. Beyond this, the precise origins of this phenomenon are as yet unclear. We share in the opinion that transition states other than **A** and **B** are unlikely to gain importance.[12]



Finally, the conversion of **4-9** to Knoevenagel-like products was readily accomplished by dissolution of the hydroxy esters in methanol, dropwise addition of small amounts of 1 N hydrochloric acid (1 mL per mmol), and vigorous stirring at ambient temperature for 8 h. The lone exception is formaldehyde. Although this reactant fares well in the initial allylation step, the subsequent conversion of **10** to **23** has not been feasible because of the inherently high reactivity of this unsaturated keto ester.

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