Pergamon

Tetrahedron Letters 40 (1999) 6535–6539

TETRAHEDRON LETTERS

Catalyzed acyl halide–aldehyde cyclocondensations. New insights into the design of catalytic cross aldol reactions

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Received 20 May 1999; revised 29 June 1999; accepted 30 June 1999

Abstract

Substoichiometric quantities (2.5–20 mol%) of $Al(SbF_6)_3$ catalyze the di(isopropyl)ethylamine-mediated cyclocondensation of various acyl halides and enolizable aldehydes to afford β-lactones in good yields (58–93%). These reactions are discussed as a strategy for executing chemo- and regiospecific catalyzed cross aldol reactions. © 1999 Elsevier Science Ltd. All rights reserved.

Considerable interest currently exists in the development of catalyzed aldol addition reactions. Despite advances in catalyzed aldol additions of latent enolate equivalents, examples of chemoselective catalyzed cross aldol reactions that require no pre-enolization, special substrate derivatization, or large molar excesses of the reaction components continue to be extremely rare.[1,2] Analysis of ketene–aldehyde cycloadditions reveals these reactions to effect the analogous C–C bond formation achieved in traditional aldol reactions, implicating these transformations as a strategy for effecting catalyzed aldol additions.[3] The β-lactone products emerging from these cycloaddition reactions constitute 'masked' aldols from which the β-hydroxy carbonyl adducts characteristic of aldol additions would emerge upon lactone ring-opening.[4] Existing procedures for ketene–aldehyde cycloadditions, however, employ laborious or expensive methods for ketene generation, thus limiting their utility as platforms for further reaction development.[5] To address this issue, Al(III)-catalyzed acyl halide–aldehyde cyclocondensation (AAC) reactions are presented herein as an operationally simple strategy for executing ketene–aldehyde cyclocondensation reactions utilizing commercially available, inexpensive reactants (Eq. 1). The β-lactones emerging from these reactions constitute acetate aldol adducts from which the characteristic β-hydroxy ester relationship is unmasked by lactone alcoholysis.

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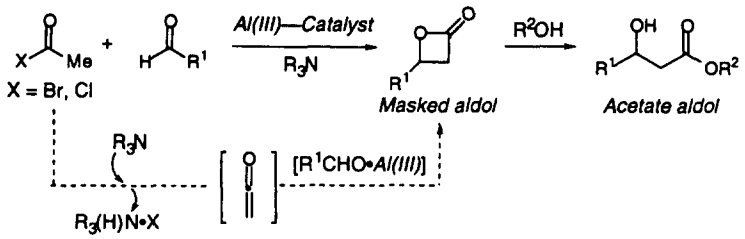
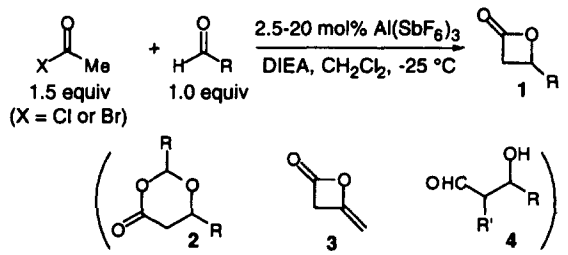
PII: S0040-4039(99)01308-8



(1)

Amine base-promoted elimination of HCl from acyl chlorides provides a convenient method for in situ ketene generation. Incorporating an aldehyde electrophile and a suitable Lewis acid into this process provides the means for catalyzing subsequent C–C bond construction in the form of a ketene–aldehyde [2+2] cycloaddition. However, previous examples of this reaction are limited to highly activated ketene precursors or non-enolizable aldehyde electrophiles.[3a,6] As a result, our preliminary AAC reaction development efforts were predicated on identifying Lewis acid catalyst–amine base combinations that afforded efficient cross coupling between aliphatic acyl halides and enolizable, non-activated aldehyde electrophiles. A typical test reaction involved addition of acetyl chloride and aldehyde (1.5:1 molar ratio) to a –25°C CH_2Cl_2 solution of Lewis acid catalyst (10–20 mol%) and a tertiary amine base (1.6 equiv. to aldehyde). From these reactions emerged variable amounts of the desired β-lactone **1**, dioxanone **2**,[7] ketene dimer (**3**), and aldehyde homoaldol **4** in ratios and yields that were particularly sensitive to the identity of the Lewis acid catalyst and the amine base (Eq. 2). Relatively unhindered amines (Et_3N, pyridine) that form acyl ammonium ions[8] upon reaction with acetyl chloride, or that would coordinate strongly to the Lewis acid complex, afforded little to no aldehyde consumption. Sterically hindered amine bases (EtN*i*-Pr_2, Cy_2NEt) delivered optimal reaction rates, presumably due to limited Lewis acid–amine base association or amine acylation. Common Lewis acids that were inefficient cyclocondensation reaction catalysts or that afforded significant quantities of the undesired reaction products (**2**, **3**, or **4**) included $BF_3 \cdot OEt_2$, $MgBr_2$, $TiCl_4$, $Cl_2Ti(O\textit{i}\text{-}Pr)_2$, $SnCl_4$, and $ZnCl_2$. Aluminum(III)-based Lewis acids, including Me_2AlCl and $Al(OTF)_3$ (20 mol%), consistently afforded higher percentages of the desired β-lactone and, as a result, were selected for further development.



(2)

Among the aluminum(III)-derived Lewis acids screened as cyclocondensation catalysts, selectivity for β-lactone formation and reaction yields increased with increasing Lewis acid strength. Accordingly, Al(III)-derived complexes incorporating highly dissociated counterions were found to be the optimum catalysts for the desired acyl halide–aldehyde cross coupling. Thus, substoichiometric quantities (2.5–20 mol%) of $Al(SbF_6)_3$ in concert with di(isopropyl)ethylamine (DIEA) constituted the most successful reaction promoter.[9,10] Under the optimized reaction conditions, the acetyl chloride–aldehyde cyclocondensations deliver the β-lactone 'cross aldol' adduct as the exclusive reaction product (≥81% yield) (Table 1).[11] Enolizable straight chain (entries a–c), α-branched (entry d), and functionalized aldehydes (entries c and e), including those possessing Lewis basic residues, are equally effective electrophiles and afford the derived β-lactone aldol adducts of sufficient purity (≥95%) to be used directly in subsequent

Table 1
Acyl halide–aldehyde cyclocondensation reactions[a]

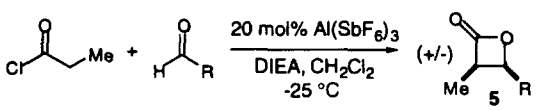
entry	Acyl Halide	Aldehyde	% yield (*cis*:*trans*)[b, c]
a	MeCOCl	$PhCH_2CH_2CHO$	93
b	MeCOCl	Me_2CHCH_2CHO	82
c	MeCOCl	$CH_2CH(CH_2)_8CHO$	81
d	MeCOCl	$C_6H_{11}CHO$	90
e	MeCOCl	$BnOCH_2CHO$	83
f	MeCOBr	$PhCH_2CH_2CHO$	60[d]
g	MeCOBr	$C_6H_{11}CHO$	58[d], 82[e]
h	EtCOCl	$CH_2CH(CH_2)_8CHO$	80 (96:4)
i	EtCOCl	$C_6H_{11}CHO$	65 (97:3)

[a]Reactions were carried out using the conditions given in reference 11 unless otherwise specified. [b]Values for chromatographically purified materials. [c]Values in parenthesis are diastereomer ratios for chromatographically pruified propionyl chloride-derived products. [d]Reaction employed 2.5 mol% $Al(SbF_6)_3$ catalyst. [e]Reaction employed 5 mol% $Al(SbF_6)_3$ catalyst.

transformations.[12] Conjugated aldehydes provide only low yields of β-lactones under these reaction conditions. No β-lactone adducts are produced in the absence of the Lewis acid, highlighting the catalyzed nature of the cyclocondensation reactions.

Efforts to reduce the requisite catalyst loadings were advanced considerably by the observation that acetyl bromide provides a considerably more reactive ketene precursor relative to acetyl chloride. As little as 2.5 mol% $Al(SbF_6)_3$ catalyzes the cyclocondensation of acetyl bromide and enolizable aldehydes to afford the derived β-lactones in 58–60% yield (Table 1, entries f and g).[13] The efficiency of the acetyl bromide–cyclohexanecarboxaldehyde cyclocondensation using 5 mol% $Al(SbF_6)_3$ (82% yield) suggests that chemical yields paralleling those obtained in the acetyl chloride experiments can be achieved using lower catalyst loadings.

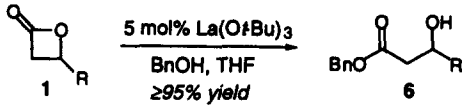
The $Al(SbF_6)_3$–DIEA reaction system also renders propionyl chloride as an effective ketene precursor in the catalyzed cyclocondensation reactions (Eq. 3). Catalyzed propionyl chloride–aldehyde cyclocondensations exhibit good levels of *cis* diastereoselection in providing the α-methyl-β-alkyl β-propiolactones **5** (R=C_6H_{11}, $(CH_2)_8CHCH_2$). The *cis*-disubstituted β-lactones **5** are obtained in high diastereomeric purity (*cis*:*trans*=≥96:4) following column chromatography (Table 1, entries h and i). These catalyzed propionyl chloride cyclocondensations represent one of a very limited number of methods for generating methyl ketene under conditions conducive to realizing cycloadditions with aldehydes.[3a]



(3)

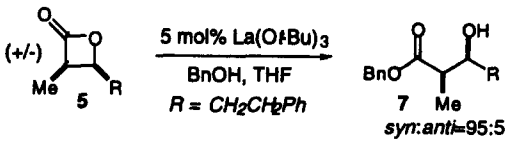
The structural homology existing between 3-substituted β-lactones and traditional acetate aldol adducts is evident upon lactone alcoholysis. We have found $La(Ot\text{-}Bu)_3$ (5 mol%) to be an efficient catalyst for ring-opening of β-lactones **1** with benzyl alcohol, affording the derived β-hydroxy esters **6** in near quantitative yields (Eq. 4).[14] The *cis*-disubstituted β-lactone **5** (R=$(CH_2)_2Ph$) undergoes analogous ring-opening to the *syn* propionate aldol **7** with complete retention of relative stereochemistry (Eq. 5).[15]

Integrating the catalyzed AAC reactions and this β-lactone ring-opening procedure provides an efficient catalytic synthesis of prototypical cross aldol adducts.



(4)

R = CH_2CH_2Ph, CH_2CHMe_2, C_6H_{11}, CH_2OBn



(5)

Aluminum tris(hexafluoroantimonate)-catalyzed AAC reactions provide an effective strategy for executing catalyzed aldol-type bond constructions. These catalyzed C–C bond constructions are characterized by their operational simplicity and the use of inexpensive, commercially available reaction components. Catalyzed AAC reactions also provide a general and easily executed synthesis of 3-substituted β-propiolactones that constitute versatile intermediates for organic and polymer synthesis.[4] The insights gained regarding salient reaction parameters and catalyst functions are expected to prove useful in continuing efforts to develop asymmetric catalytic variants of the cyclocondensation reactions.

Acknowledgements

The University of Pittsburgh and the National Science Foundation (CHE-9875735) are gratefully acknowledged for support of this work.

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9. The molecular formula for $Al(SbF_6)_3$ represents the $AlCl_3$:$AgSbF_6$ stoichiometry (1:3) used to generate the catalyst complex; the structure of the resulting catalyst complex was not rigorously established.
10. Aluminum(III) triflate and $Zr(SbF_6)_4$ (derived from 1 $ZrCl_4$:4 $AgSbF_6$) were also effective reaction catalysts for certain aldehyde substrates. However, these catalyst complexes were not as generally useful as $Al(SbF_6)_3$.
11. Typical experimental procedure: To a –25°C solution of $AlCl_3$ (0.20 mmol) and diisopropylethylamine (0.60 mmol) in 1.5 mL of CH_2Cl_2 was added a solution of $AgSbF_6$ (0.60 mmol) in 1.5 mL of CH_2Cl_2. To the resulting heterogeneous mixture was added the DIEA (1.0 mmol), acid chloride (1.5 mmol), and aldehyde (1.0 mmol) and the reaction stirred at –25°C until complete as monitored by TLC (3–5 h). The reaction mixture was eluted through a silica gel pad with CH_2Cl_2 and the product was isolated by column chromatography (hexanes:ethyl acetate).
12. The β-lactones are uniformly the only products present upon GC or $^1H/^{13}C$ NMR analysis of the crude reaction mixtures (≥95% purity). Under the optimized reaction conditions, no traces of aldehyde homoaldol products could be detected.
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