Organic LETTERS

Letter

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Thiol-Promoted Selective Addition of Ketones to Aldehydes

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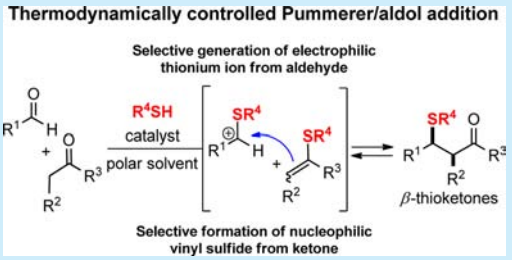
Supporting Information

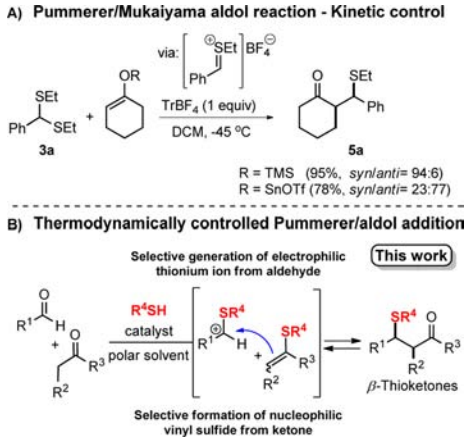
ABSTRACT: A simple and efficient thiol-mediated addition of ketones to aromatic and aliphatic aldehydes is reported. This thermodynamically controlled Pummerer/aldol reaction, which can tolerate both moisture and protic functional groups, provides a direct entry to *syn*-β-thioketones in high chemo- and regioselectivity. Mechanistic studies revealed that selective transformation of the aldehyde to an electrophilic thionium ion species concurrent with the generation of a nucleophilic vinyl sulfide coupling partner from the ketone is imposing cross-coupling over dimerization.



The aldol reaction is one of the most important C−C bond forming reactions in synthetic organic chemistry.[1] Having an advanced to high level of sophistication, this reaction is widely applied in the synthesis of polyoxygenated natural products.[1a] Nonetheless, the required chemo-, regio-, and stereoselectivity has been achieved only via kinetically controlled conditions, and in most cases full enolization of the ketone prior to the addition of the aldehyde is needed. This step demands a stoichiometric amount of activators (base, metal, etc.) and stringent conditions (such as low temperature, anhydrous solvents) that render the entire process burdensome. A search is therefore underway for methods that will enable the selective enolization of ketones in the presence of enolizable aldehydes and other acidic functionalities. While organocatalysts based on secondary amines can partially meet this challenging goal,[2] to the best of our knowledge, the exploitation of nucleophilic vinyl sulfides as a surrogate for the enol group has not been explored, although evidence for such reactivity can be found in the literature.[3] Herein, we report that thiols mediate the cross-addition of aromatic and aliphatic aldehydes to ketones. Under these conditions, all the reaction steps are reversible, thereby enabling coupling between the nucleophilic vinyl sulfide[4] formed selectively from the ketone and the electrophilic thionium ion species generated from the aldehyde (Scheme 1B). Their coupling in polar solvents and in the presence of Lewis or Brønsted acid catalysts provides a direct entry to *syn*-β-thioketones[5] with high chemo- and regioselectivity. This elegant and sustainable C−C bond forming reaction can tolerate both moisture and protic functional groups.

The reactivity of thionium ions toward nucleophiles has been extensively studied and applied in numerous C−C bond forming reactions for over a century.[6,7] Usually, the formation of thionium ions from sulfoxides (the Pummerer reaction)[7a−d,g] or dithioacetal[7h−j] or directly from aldehydes and thiols (Connective Pummerer)[7k−p] requires stoichiometric amounts of an activator [such as Ac_2O, Tf_2O, TMSCl, dimethylmethylthiosulfonium fluoroborate (DMTSF)[7h,i]] and/or strong Lewis acids [$TiCl_4$, $SnCl_2$, $Hg(OAc)_2$], thereby limiting the reaction to nucleophiles that are unreactive toward the activators.

Scheme 1. (A) Pummerer/Mukaiyama Aldol Addition and (B) Pummerer/Aldol Reaction (This Work)



Moreover, under these conditions the process is irreversible, and therefore the side reactions that result from attack of the thionium ion by competitive nucleophiles affect the reaction's efficiency (for example, Pummerer rearrangement).

The addition of thionium ions to enol ethers is an important variation of the Mukaiyama aldol reaction, which has been studied by several groups.[1c,4b,8] The Mukaiyama group investigated the coupling of the dithioacetal of benzaldehyde **3a** to Sn(II) enolate or the TMS-enol ether of cyclohexanone with a stoichiometric amount of triphenylcarbenium tetrafluoroborate ($TrBF_4$) as the activator (Scheme 1A).[9] The stereochemistry of the products was not determined at the time, but the current study confirmed that the addition of dithioacetal **3a** to tin enolates is *anti*-selective (23:77), while that to TMS-enol ethers is highly *syn*-selective (94:6). In the current study, we explored the possibility of developing a

Received: October 4, 2014
Published: November 6, 2014

dx.doi.org/10.1021/ol502937n | *Org. Lett.* 2014, 16, 5922−5925

thermodynamically controlled addition reaction of aldehydes and ketones mediated by thiols (Scheme 1B).

First, we screened for suitable reaction conditions. The experiments included mixing of benzaldehyde **1a** (1 equiv), cyclohexanone **2a** (3 equiv), and ethanethiol (3 equiv) under different sets of conditions. Examination of the different solvents across the polarity spectrum [copper(II) trifluoromethanesulfonate (5 mol %),[10] rt] showed that the thioacetalation steps proceeded smoothly in most organic solvents, with the exception of DMF and DMSO (Figure 1),

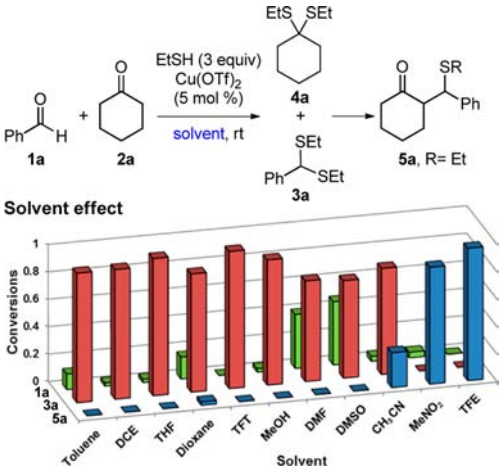
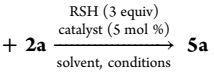


Figure 1. Reaction solvent screening. Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), EtSH (0.6 mmol), catalyst (5 mol %), solvent (0.3 M), rt, 6 h; the products' molar ratios were determined by HPLC analysis using mesitylene as the internal standard. DCE = 1,2-dichloroethane, THF = tetrahydrofuran, TFT = α,α,α-trifluorotoluene, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, TFE = 2,2,2-trifluoroethanol.

but β-thioketone **5a** was formed only in acetonitrile, nitromethane, and 2,2,2-trifluoroethanol (TFE), all polar solvents with high dielectric constants that are capable of stabilizing charge separation. Experimentation with different catalysts (see Figure S1B in the Supporting Information (SI)) showed that hard Lewis acids, such as $CuCl_2$, $Sc(OTf)_3$, $Fe(OTf)_3$, $In(OTf)_3$, $BF_3{\cdot}OEt_2$, and $Cu(OTf)_2$, promoted the reaction, while softer Lewis acids [CuBr, $Zn(OTf)_2$, $Ni(OTf)_3$, and $Fe(OTf)_2$] and Brønsted acids, such as *p*-toluenesulfonic acid (PTSA) and acetic acid, were not effective. On the other hand the reaction with trifluoromethanesulfonic acid (TfOH, 5 mol %) reached full conversion. For reasons of ease of handling $Cu(OTf)_2$ was chosen as the catalyst for further investigation.

The initial screening identified conditions that produced β-thioketone **5a** in 76% yield, but with moderate diastereoselectivity (Table 1, entry 1). Further studies revealed that both the stereoselectivity and the efficiency of the process were temperature dependent (Table 1, entries 1−3). A change of the solvent from nitromethane to TFE improved both the yield (92%) and the diastereomeric product ratio (*syn*/*anti* = 5.5:1; Table 1, entry 5) of the reaction. When the reaction was carried out at −40 °C with 2 equiv of TfOH, high selectivity (*syn*/*anti* = 11:1; Table 1, entry 6) was obtained. Other thiols may also be used (Table 1, entries 9−11), while ethanethiol was found to be the most effective. Notably, compounds **5a**−**d** were obtained as single products, and other possible side products, such as bis-aldol addition or condensation products, were not observed.[3]

Table 1. Optimization of Reaction Conditions[a]



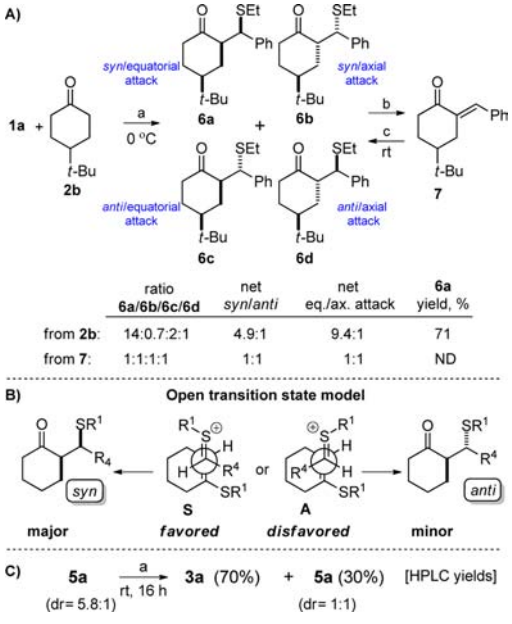
1a + **2a** → **5a** (R = Et)

entry	catalyst	R	solvent	conditions	**5a** [%][b]	*syn*/*anti*[c]
1	$Cu(OTf)_2$	Et	$MeNO_2$	rt, 6 h	76	4.3:1
2	$Cu(OTf)_2$	Et	$MeNO_2$	0 °C, 24 h	NR[d]	–
3	$Cu(OTf)_2$	Et	$MeNO_2$	80 °C, 4 h	70	1:1
4	$Cu(OTf)_2$	Et	TFE	rt, 2 h	94	5.5:1
5	$Cu(OTf)_2$	Et	TFE	10 °C, 6 h	92	5.5:1
6[e]	TfOH	Et	TFE	−40 °C, 2 h	85	11:1
7	$In(OTf)_3$	Et	TFE	rt, 6 h	80	7.1:1
8	$Sc(OTf)_3$	Et	TFE	rt, 6 h	75	7.1:1
9	$Cu(OTf)_2$	^{i}Pr	TFE	rt, 6 h	**5b**, 84	2.5:1
10	$Cu(OTf)_2$	Bn	TFE	rt, 18 h	**5c**, 64	7.1:1
11	$Cu(OTf)_2$	Ph	TFE	rt, 6 h	**5d**, 51	1:1
12	$Cu(OTf)_2$	–	$MeNO_2$	60 °C, 24 h	NR[d]	–

[a]Conditions: benzaldehyde **1a** (1 equiv), cyclohexanone **2a** (3 equiv), thiol (3 equiv), and $Cu(OTf)_2$ (5 mol %) in nitromethane or TFE (0.3 M). [b]Isolated yield of pure product. [c]The diastereomeric ratio was determined by ^{1}H NMR. [d]NR = no reaction. [e]TfOH (200 mol %) was used.

The next set of experiments were performed to probe the reaction mechanism and to clarify the stereochemical aspects of this multicomponent transformation. In the absence of ethanethiol both benzaldehyde **1a** and cyclohexanone **2a** were recovered (Table 1, entry 12). Thus, the possibility that the reaction proceeded via an aldol condensation/Michael addition pathway was ruled out.[11] 4-*tert*-Butylcyclohexanone **2b** was chosen for modeling the attack direction of the thionium ion species (Scheme 2A). In principle, four diastereoisomers **6a** (*syn*/equatorial attack), **6b** (*syn*/axial attack), **6c** (*anti*/

Scheme 2. Mechanistic Study of the Addition of Aromatic Aldehydes and Cyclohexanone Derivatives[a]



[a]Conditions: (a) EtSH (3 equiv), $Cu(OTf)_2$ (5 mol %), TFE. (b) NaOH, EtOH−H_2O (3:1), rt, 1.5 h, quantitative. (c) Similar conditions to a, except that $MeNO_2$ was used as the solvent.

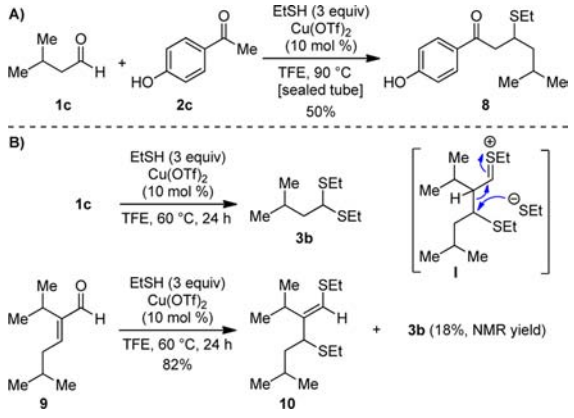
dx.doi.org/10.1021/ol502937n | *Org. Lett.* 2014, 16, 5922−5925

equatorial attack), and **6d** (*anti*/axial attack) could have been formed in this reaction. In practice, a moderate degree of net *syn*-selectivity [(**6a** and **6b**)/(**6c** and **6d**), *ca.* 4.9:1) and a high preference for attack from the equatorial direction [(**6a** and **6c**)/(**6b** and **6d**), *ca.* 9.4:1)] were observed. Overall, *β*-thioketone **6a** was isolated in 71% yield after column chromatography. The possibility that this selectivity derives from the difference in stability of the isomers was ruled out, since the thia-Michael addition of ethanethiol to 2-benzylidene-4-(*tert*-butyl)cyclohexanone (**7**) under similar reaction conditions [$Cu(OTf)_2$ (5 mol %), rt] was found to be nonselective in $MeNO_2$, affording the four diastereoisomers **6a**−**d** in equal ratios, and inefficient in TFE.

Based on steric arguments and previous findings, it may be assumed that the ethyl group of the thionium ion is *cis* to the H-atom (Scheme 2B).[8f] The fact that similar stereoratios are observed for different Lewis and Brønsted acids suggests that the catalysts are not intimately involved with the thionium ion during the transition states.[1c] Therefore, an open transition state model[8f,12] is more likely. It is suggested that nonbonded interactions between R^4 of the thionium ion and the cyclohexane ring in TS **A** (giving the *anti*-product) cause a destabilizing effect, which favors the *syn*-product through TS **S**. This C−C bond forming step is highly selective and leads to high diastereoselectivity under kinetic conditions (low temperature for short reaction time, as in Table 1, entry 6). Yet, under thermodynamic conditions (a prolonged reaction time at a temperature >0 °C), the stereochemical outcome is significantly affected due to several reversible processes. Elimination of the thiol group from the product followed by nonselective thia-Michael addition is a major concern.[13] Another destructive process is the retro-addition cleavage to return starting materials. When the reaction's product *β*-thioketone **5a** (initial dr = 5.8:1) was resubmitted to the reaction conditions, dithioacetal **3a** was detected by HPLC analysis in 70% yield together with a 30% yield of **5a** (dr = 1:1, Scheme 2C).

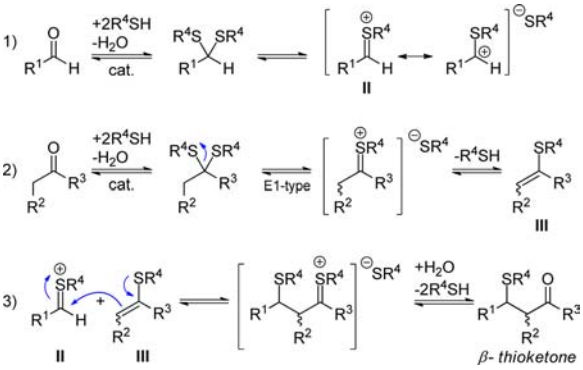
Next, the Pummerer/aldol addition of aliphatic aldehydes to ketones was examined. It would be quite advantageous to couple ketones with aliphatic aldehydes, since the aldol addition of ketones to aliphatic aldehydes is not favorable from both thermodynamic and kinetic points of view, and in most cases this reaction resulted exclusively in self-coupling of the aldehyde. Indeed, this result was obtained when isovaleraldehyde **1c** was reacted with 4′-hydroxyacetophenone **2c** in the absence of thiol [$Cu(OTf)_2$, $MeNO_2$, rt]. However, the addition of ethanethiol changed the mechanistic scheme, and the cross-addition product **8** was isolated in 50% yield [$Cu(OTf)_2$ (10 mol %), TFE, 90 °C, sealed tube, Scheme 3A]. The foundations for this significant chemoselective process are based on prior observations by the Cohen group, who reported that the elimination of thiophenol from dithioacetals of ketones to form vinyl sulfides takes place several orders of magnitude faster than its elimination from dithioacetals of aldehydes.[14] The rate of this E1-type elimination depends on the stability of the carbonium ion that remains after the loss of one thiol group.[15] To further probe this unique chemoselectivity, aldehyde **1c** was mixed with ethanethiol under similar reaction conditions (rt to 60 °C, 24 h). GC-MS and NMR analyses of the crude reaction products (see SI) revealed that dithioacetal **3b** was formed almost exclusively with only a trace amount of homodimerization products (Scheme 3B). In contrast, when 2-isopropyl-5-methyl-2-hexenal (**9**), which is the self-aldol condensation

Scheme 3. Addition of Aliphatic Aldehydes to Ketones



product of **1c**, was reacted with ethanethiol [$Cu(OTf)_2$ (10 mol %), TFE, 60 °C, 5 h], dithioacetals **10** and **3b** were obtained in a 4.6:1 ratio. The formation of **3b** from **10** may take place via thionium ion intermediate **I**. These experiments suggest that the homocoupling of dithioacetal **3b** is both kinetically unfavorable and reversible under the reaction conditions, emphasizing the mechanistic distinction between this three-component addition reaction and the classic aldol reaction. Overall, we propose that the formation of an electrophilic thionium ion **II** (Scheme 4, eq 1) from the aldehyde and the

Scheme 4. Proposed Mechanism



concurrent selective generation of a nucleophilic vinyl sulfide **III** from the ketone (Scheme 4, eq 2) are the key factors that dictate the unusual chemoselectivity observed in this reaction.

Finally, we set out to investigate the scope of this unique thiol-mediated reaction (Figure 2). It is clear that both electron-deficient and -rich aromatic aldehydes are suitable coupling partners. The addition of benzaldehyde **1a** to 3-methylcyclohexanone at low temperature afforded product **15** (77% yield) in high regioselectivity, and the coupling of **1a** with 2-methylcyclohexanone under kinetic conditions (−40 °C) took place at C-6 affording compound **16a** in 70% yield (dr = 1:1:5:12), whereas, under thermodynamically controlled conditions (rt) a mixture of two regioisomers **16a** (34% yield, dr = 0:1:2:31) and the C-2 substitution product, **16b** (24% yield, single isomer), were obtained. In general, the addition of aliphatic aldehydes required harsher conditions, as the reactions failed to reach full conversion (compounds **14**−**15** and **26**−**27**). Importantly, protic functional groups, such as −OH (products **21a**, **25**−**26**) and CO_2H (**23**), did not require any protection.

dx.doi.org/10.1021/ol502937n | *Org. Lett.* 2014, 16, 5922−5925

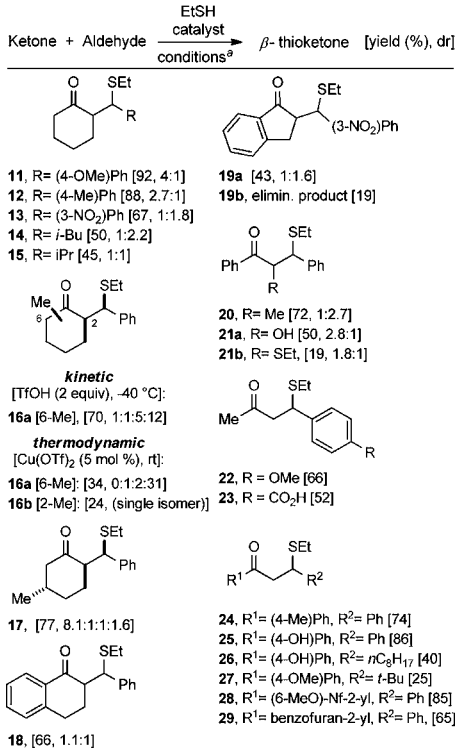


Figure 2. Substrates scope. For the exact reaction conditions, see SI.

In summary, a simple and efficient thiol-mediated addition of ketones to aromatic and aliphatic aldehydes was developed. There are several reasons why this Pummerer/aldol reaction is unique. Namely, both aldehyde and ketone coupling partners are selectively activated by the same thiol. The incorporation of vinyl sulfide as a surrogate for enolate eliminates the need to activate the ketone in advance. The reaction exhibits a distinctly mechanistic scheme compared to the classic aldol reaction, with all steps being reversible. This method provides a single-step process for the synthesis of important β-thioketone building blocks.[16] Finally, this multicomponent process can be carried out in air in the presence of water and protic functional groups (protective groups are not needed).

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†R.P. and S.N. contributed equally.

Notes

The authors declare no competing financial interest.

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