Highly Enantioselective Intermolecular Stetter Reactions of β -Aryl Acceptors: α -Ketoester Moiety as Handle for Activation and Synthetic Manipulations

2011 Vol. 13, No. 18 4942–4945

ORGANIC LETTERS

Eduardo Sánchez-Larios,[†] Karen Thai,[†] François Bilodeau,[‡] and Michel Gravel^{*,†}

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada, and Research and Development, Boehringer Ingelheim (Canada) Ltd., 2100 rue Cunard, Laval, QC H7S 2G5, Canada

michel.gravel@usask.ca

Received July 28, 2011

ABSTRACT



The use of β , γ -unsaturated- α -ketoesters in the intermolecular Stetter reaction furnishes 1,2,5-tricarbonyl compounds in high yield and excellent enantioselectivity. The α , δ -diketoesters generated using this methodology serve as useful synthetic building blocks via chemo- and diastereoselective transformations.

Organic transformations catalyzed by *N*-heterocyclic carbenes (NHCs) have been an area of intensive research in recent years.¹ The Stetter reaction was first disclosed in 1973 and consists of the addition of an aldehyde-derived acyl anion equivalent onto an electron-poor olefin (eq 1).²



Ever since, several research groups have worked intensively toward the development of enantioselective versions of this transformation. In 1996, Enders and co-workers reported the first enantioselective *intramolecular* Stetter reaction.³ This pioneering work inspired others to develop highly efficient catalysts and protocols achieving high levels of enantioselectivity.^{4,5} However, the *intermolecular* version of the Stetter reaction remains a challenge. Enders and co-workers reported the first intermolecular

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[†] University of Saskatchewan.

[‡]Boehringer Ingelheim (Canada) Ltd.

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enantioselective Stetter reaction, albeit delivering the product in low yield (4%) and enantioselectivity (39% ee).⁶⁻⁸ In 2008, the same group reported an improved intermolecular Stetter reaction with moderate enantioselectivities (up to 78% ee, Figure 1).



Figure 1. Acceptors previously used in enantioselective intermolecular Stetter reactions.

Their work involved the use of either chalcone derivatives⁹ or arylidenemalonates¹⁰ as acceptors with N-benzyl triazolium precatalyst 1a. Concurrently, Rovis and co-workers employed alkylidenemalonates as acceptors in combination with highly reactive glyoxamides in the presence of N-aryl triazolium precatalyst 1b.¹¹ This seminal contribution disclosed the first examples of highly enantioselective intermolecular Stetter reactions (up to 91% ee). This work was followed by an enantio- and diastereoselective intermolecular Stetter reaction using alkylidene ketoamides achieving high levels of diastereo- and enantioselectivity (up to 19:1 dr and 98% ee).¹² In 2009, the same group disclosed a remarkable study on the design of the backbone-fluorinated NHC 1c.¹³ This newly designed organocatalyst improved the enantioselectivities up to 96% ee when β -alkyl nitroalkenes were used as Stetter acceptors.¹⁴ Very recently, the research group led by Glorius reported a highly enantioselective synthesis of amino acids (up to 99% ee) by means of intermolecular Stetter reactions using β -unsubstituted acrylates. In contrast to the other manifolds, the key feature of this approach is a diastereoselective proton transfer during the Stetter reaction.¹⁵

Despite these great advances in the area, several limitations remain. Most importantly, the use of β -aryl substituted acceptors has not yet afforded synthetically useful yields of

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highly enantioenriched ($\geq 90\%$ ee) products.¹⁶ An added difficulty with the use of these acceptors is the ease of racemization of the resulting products under the basic reaction conditions.¹⁷ In addition, simple α . β -unsaturated ketone acceptors have not delivered enantioenriched Stetter products with high efficiency.¹⁶ This shortcoming stands in contrast to the widespread use of ketone acceptors in combination with achiral catalysts.² In order to address these issues. we decided to investigate the use of β , γ -unsaturated- α ketoesters¹⁸ as acceptors for the intermolecular Stetter reaction. We reasoned that the highly electrophilic nature of these acceptors would allow us to explore a wide range of catalysts under mild conditions. Interestingly, the α -ketoester products obtained constitute a known family of cysteine protease inhibitors.¹⁹ In addition, the unique functionalities present in the resulting Stetter products would provide an ideal venue for a variety of useful synthetic transformations.

We began our studies by comparing the reactivity of a model acceptor (3a) with two other phenyl-substituted acceptors, *trans*-chalcone (5) and β -nitrostyrene (6) (Scheme 1).

Scheme 1. Competition Reactions Between Model Acceptor 3a and *trans*-Chalcone (5) or β -Nitrostyrene (6)



Each competition reaction was performed in the presence of a thiazolium precatalyst and furfural (2a) as the limiting reagent. Remarkably, the model acceptor 3a proved to be at least 20 times more reactive than *trans*chalcone and β -nitrostyrene under these conditions, based on the fact that 4a was the only product that could be detected by ¹H NMR spectroscopy upon complete consumption of furfural.

We then set out to find the optimal conditions employing the model acceptor **3a** in combination with furfural (**2a**) (Table 1).

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Table 1. Optimization of the Reaction^a



^{*a*} Unless otherwise noted, all reactions were performed by addition of the base to a solution of **2a** (1.5 equiv), **3a**, and precatalyst in the appropriate solvent (0.2 M) at 0 °C. ^{*b*} Yield of pure isolated products. ^{*c*} Enantiomeric excess determined by HPLC analysis. ^{*d*} The opposite enantiomer was obtained. ^{*e*} One equivalent of *i*Pr₂NEt was used. DBU = 1,8-diazabiciclo[5.4.0]undec-7-ene

The screening of bases and solvents in the presence of an achiral triazolium salt led us to find N.N-diisopropylethylamine (*i*Pr₂NEt) and dichloromethane (CH₂Cl₂) as the optimum base and solvent (see Supporting Information). With this set of reaction conditions, various chiral triazolium salts were evaluated. Rovis' aminoindanol-derived triazolium salt $1e^{20}$ gave poor yield and enantioselectivity (Table 1, entry 1). The structurally related and bulkier catalyst 1f proved to be unreactive under our reaction conditions (entry 2). Rewardingly, the desired product was obtained in good yield and good enantioselectivity when catalyst 1g¹³ was used (entry 3). As was also observed by Rovis et al. using nitroalkene acceptors,¹³ fluorinated triazolium 1c substantially improved the enantioselectivity relative to triazolium 1g (entry 4).²¹ It was also found that a stoichiometric amount of base was required with this catalyst in order to achieve complete conversion. Interestingly, it was also found that a reduction in the catalyst loading noticeably improved the enantiomeric excess (entries 5-6). Further reduction of the loading to 1 mol % proved to be detrimental (entry 7).

Thereafter, we studied the scope of the reaction (Scheme 2). First, we investigated a variety of aldehydes in the presence of the model acceptor **3a**. When 5-methylfurfural (**2b**) was employed, the reaction proved to be slower than the one using furfural (**2a**) (4.5 h vs 15 min, respectively). In both cases, the corresponding benzoin product was formed instantaneously. In the case of **2b**, subsequent conversion of the benzoin product to the desired Stetter product was found to be slower than for **2a**, possibly due to

the electron-donating effect of the methyl group on the heteroaromatic ring. When the aromatic aldehyde methyl 4-formylbenzoate (**2c**) was used, the reaction proceeded to form **4c** in low yield and moderate enantioselectivity.²² The use of pyridine-2-carboxaldehyde (**2d**) led to a more selective reaction (forming **4d**) than the one using pyrazine-2-carboxaldehyde (**2e**) (91 vs 87% ee). Remarkably, when quinoline-2-carboxaldehyde (**2f**) was employed, it furnished Stetter adduct **4f** in excellent yield and very high enantioselectivity (>98% ee).

Scheme 2. Scope of the Reaction^{*a*}



^{*a*} General reaction conditions: **2** (0.15 mmol), **3** (0.1 mmol), **1c** (5 mol %), *i*Pr₂NEt (0.1 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C for < 5 min - 4.5 h. Yields of pure isolated products. Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. The absolute configuration was tentatively assigned by analogy to ref. 13.

^b 10 mol % of **1c** was required.

Subsequently, the scope of the acceptor was studied. The use of electron-poor aromatic groups such as 4-fluorophenyl (4g) and 4-bromophenyl (4h) gave excellent enantioselectivity. Similarly, the use of an electron-withdrawing meta-methoxy substituent resulted in an increased reactivity on the acceptor (3i), generating the desired product 4i in excellent yield and enantioselectivity. The addition of an electron-donating *para*-methoxy substituent to this acceptor did not adversely affect the reactivity or selectivity, furnishing adduct 4i. The larger naphthalene substituent on 3k was well tolerated, producing 4k in excellent yield and selectivity. Heteroaromatic-substituted acceptors can also be used, as shown by product 41, which was obtained in good yield and high enantioselectivity. These reactions can also be scaled up. Indeed, the Stetter reaction yielding 4a was reproduced on ca. 3 mmol of acceptor 3a with similar results, provided that the

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⁽²²⁾ Rovis and co-workers have observed that benzaldehyde fails to react in the presence of β -alkyl nitroalkenes and **1c**. See ref 13.

base was added dropwise as a solution in CH_2Cl_2 . Another remarkable feature of this methodology is the very short reaction time associated with high enantioselectivities (usually < 5 min).

The α, δ -diketoesters generated enantioselectively through our procedure serve as excellent building blocks that can undergo further chemo- and diastereoselective transformations. We envisioned that each carbonyl group could be manipulated chemoselectively due to their different electronic properties. For this part of the study, 4a was chosen as model substrate. The first transformation was performed with L-Selectride or Super-Hydride to reduce the more electrophilic site, furnishing the alcohol 7a with excellent yield and essentially complete diastereoselectivity (Scheme 3). Examples of diastereoselective reductions of 1,4-dicarbonyl compounds directed by a 2-aryl or alkyl substituent are very rare.²³ Importantly, HPLC analysis of alcohol 7a confirmed that reduction of the Stetter adduct occurred without erosion of the enantiomeric excess. The single reduction product 7a could be further functionalized to the N-protected amino ester derivative 8a in moderate yield (unoptimized). Double reduction of the ketone functionalities yielded the corresponding diols 9a and 9h in excellent yield. Again, the α ketoester was reduced with high diastereoselectivity (>20:1) whereas the aromatic ketone was reduced with good Felkin selectivity (3-8:1). The brominated diol 9h was further transformed into the 2,3,5-trisubstituted tetrahydrofuran 10h under mildly acidic conditions. Presumably, this transformation occurs though an S_N1 mechanism furnishing the more thermodynamically stable 2,3-trans product. Compound 10h was employed to determine the relative configuration at C3 and C5 via NOE experiments (see Supporting Information for details). Complete reduction of the three carbonyl groups was accomplished by consecutive reduction to the 2,5-diol followed by reduction of the ester using LiAlH₄. The resulting triol was used without further purification and subjected to oxidative cleavage of the diol to afford the hemiacetal 12a. This hemiacetal could be further oxidized with PCC to the 3,4-disubstituted lactone 13a in 95% yield. The observed 3,4-cis relative configuration confirms the stereochemical outcome of the second reduction of 4a,h affording 9a,h and 11a (see Supporting Information).

In conclusion, we are reporting the first high yielding and highly enantioselective intermolecular Stetter reactions on β -aryl substituted acceptors, thus complementing current Scheme 3. Chemo- and Diastereoselective Transformations on $\alpha,\delta\text{-Diketoesters}$ 4a and 4h



methodologies. This method is operative with a variety of heteroaromatic aldehydes and aromatic or heteroaromatic acceptors. In addition, this represents a useful method to prepare 1,2,5-tricarbonyl compounds, which are amenable to a variety of synthetic transformations delivering α -hydroxy esters, α -amino acid derivatives, 2,5-dihydroxyesters, 2,3,5-trisubstituted tetrahydrofuran derivatives, and 3, 4-disubstituted lactones. Studies aimed at widening the scope to less reactive aldehydes (aliphatic and aromatic) and γ -alkyl acceptors are currently underway.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant to M.G.), the Canada Foundation for Innovation, the University of Saskatchewan, and Boehringer Ingelheim (Canada) Ltd. (Industrial Cooperative Research Scholarship in Synthetic Organic Chemistry to K.T.) for financial support.

Supporting Information Available. Spectroscopic data (¹H and ¹³C NMR) and detailed experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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