Tetrahedron 73 (2017) 3643–3651

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Scalable synthesis of enaminones utilizing Gold's reagents

Alexander W. Schuppe, James M. Cabrera, Catherine L.B. McGeoch, Timothy R. Newhouse*

Department of Chemistry, Yale University, 275 Prospect Street, New Haven, CT 06520-8107, United States

ARTICLE INFO

Article history:
Received 16 February 2017
Received in revised form
27 March 2017
Accepted 31 March 2017
Available online 2 April 2017

Keywords:
Enaminones
Rawal diene
Diels-Alder

ABSTRACT

Several Gold's reagents were synthesized from cyanuric chloride and *N,N*-dialkylformamides. These synthetic equivalents of *N,N*-dimethylformamide dimethyl acetal were used in an optimized and scalable procedure for the regioselective synthesis of a variety of enaminones from ketone starting materials, whose utility was demonstrated by the stereoselective synthesis of Rawal-type dienes.

1. Introduction

The use of dienes with electron-donating groups in the Diels-Alder reaction leads to increased rates of reaction, thus allowing for more mild reaction conditions and broader functional group compatibility.[1] In particular, Danishefsky- and Rawal-type dienes,[2,3] which possess two constructively oriented electron-donating groups, have been widely used in natural product synthesis.[4,5] This is because of their ease of preparation, increased reactivity toward thermal cycloadditions, and the utility of the oxidation states introduced as the heteroatom substituents.[2,3] Both of these types of dienes have been conveniently prepared by enolization and trapping of a β-substituted enone – a β-methoxy enone in the case of Danishefsky dienes and an enaminone for Rawal dienes.[2,3]

Enaminones, which are also powerful building blocks for heterocycle formation and Michael addition-elimination reactions,[6–10] are usually accessed through functionalization of a ketone directly with *N,N*-dimethylformamide dimethyl acetal (**2**, DMF-DMA)[11] or Bredereck's reagent (**3**)[12] as shown in Fig. 1a. While this approach is simple and direct, it can lead to non-selective enolization and thus constitutional isomeric products wherein the two different ketone α-positions have been functionalized (e.g. **4a** and **4b**). This problem has been circumvented through stepwise enone formation via β-elimination of an acetal formed from trimethylorthoformate, followed by addition-elimination with dimethylamine (Fig. 1b).[13] It is

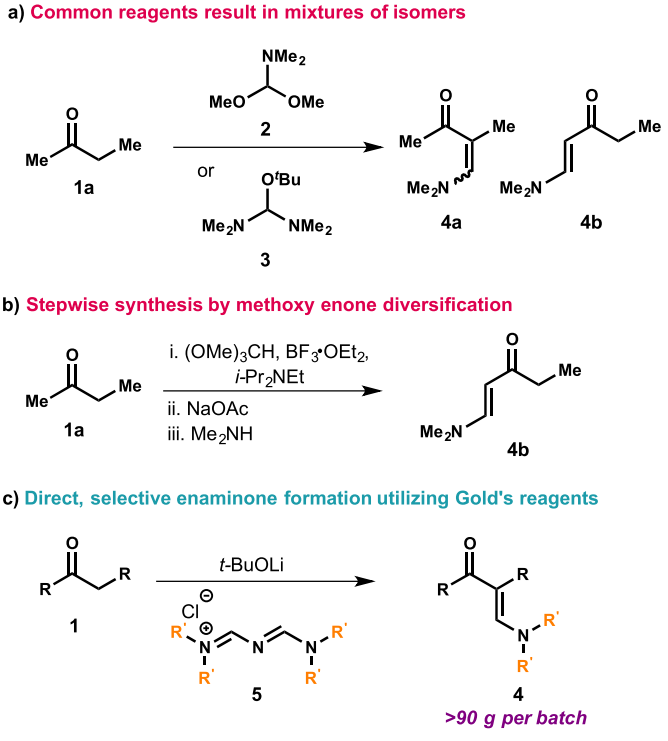


Fig. 1. Enaminone formation from ketones by multiple approaches.

* Corresponding author.
E-mail address: timothy.newhouse@yale.edu (T.R. Newhouse).

http://dx.doi.org/10.1016/j.tet.2017.03.092
0040-4020/

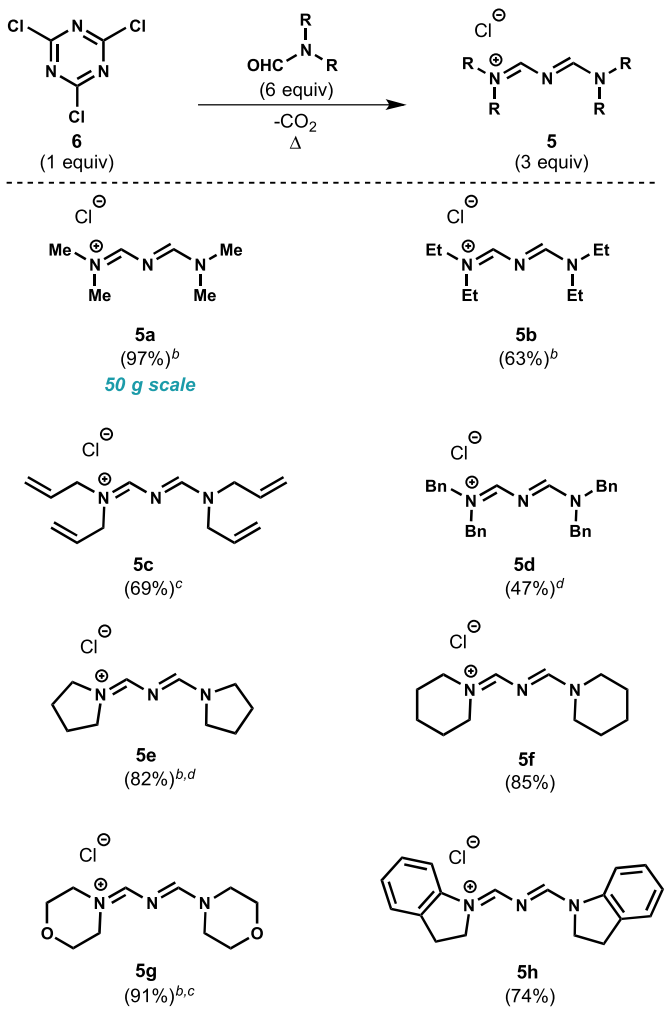
noteworthy that this latter approach allows for the synthesis of a wide variety of β-amino substituted enones from a single β-methoxy enone precursor.

During the course of a total synthesis of andirolide N,[14] we examined these conventional approaches for enaminone synthesis and ultimately found the most scalable approach utilized the aminomethylene electrophile equivalent (**5**), known as Gold's reagent.[15–17] This approach allowed for the direct regio- and diastereoselective functionalization of 2-butanone using Gold's reagent, a bench stable reagent which can be prepared in a single step and purified by recrystallization.[17] The straightforward preparation of this valuable equivalent to DMF-DMA employs inexpensive cyanuric chloride and DMF. In this report we describe the synthesis of a small library of sterically and electronically varied Gold's reagents using readily available formamides, and investigate their utility in enaminone synthesis.

2. Results and discussion

2.1. Synthesis of a library of Gold's reagents

In order to expand the synthetic utility of Gold's reagents, various [3-(dialkylamino)-2-azaprop-2-en-1-ylidene]dialkylammonium chloride salts (**5**) were synthesized, and an improved procedure for the preparation of the tetramethyl analog (**5a**) was developed.[17] The synthesis of these reagents proceeded smoothly by heating one equivalent of cyanuric chloride (**6**) and six equivalents of *N,N*-dialkylformamide, either neat or using 1,4-dioxane as solvent (**5a**, **5b**, **5e**, and **5g**), to produce three equivalents of the corresponding Gold's reagent (**5**, Scheme 1). It should be noted that during the course of this exothermic reaction three equivalents of CO_2 are produced, and thus caution should be exercised when this reaction is performed on large scale.



Scheme 1. Formation of Gold's reagents using formamides[a-d]. [a]Isolated yield. [b]1,4-dioxane was used as solvent (4 M). [c]3 equiv of formamide was used. [d]4 equiv of formamide was used.

Careful control of the temperature was critical for minimizing byproduct formation during the exothermic release of CO_2. Concomitant with the release of CO_2 was a distinct change in color of the reaction mixture to a dark red or brown, occurring at a different temperature for each substrate. As a precaution, a modified protocol involving a double-walled reflux condenser and an oil-bubbler outlet was employed (see Supplementary Materials) for the scalable synthesis of the parent methyl-substituted Gold's reagent (**5a**). While this procedure was successful on a 50-g scale to provide 120 g of **5a** in 97% yield, further optimization is likely necessary for larger scale preparations due to the exotherm and gas release.

Using this protocol, a number of Gold's reagents could be prepared, as depicted in Scheme 1. Ethyl substitution on the formamide yielded the corresponding ethyl Gold's reagent (**5b**) in 63% yield. Activated alkyl substituents, such as allyl (**5c**) and benzyl (**5d**), were also tolerated in the synthesis of the corresponding Gold's reagents in 69% and 47% yield, respectively. The synthesis of several reagents derived from cyclic formamides proceeded well: pyrrolidine (**5e**), piperidine (**5f**), morpholine (**5g**), and indoline (**5h**) Gold's reagents were synthesized in 74–91% yield. In order to observe complete conversion for some of the more challenging substrates (**5c**, **5d**, **5e**, and **5g**), fewer equivalents of the formamide were used relative to cyanuric chloride. Purification of the Gold's reagents could be readily performed by simple trituration with combinations of ethereal and hydrocarbon solvents.

2.2. Development of optimized conditions for the transformation of ketones to enaminones

With a library of novel Gold's reagents in hand, we turned to optimization of the conditions for enaminone formation (Table 1). Previous conditions described by Gupton and co-workers[16a] employed using the newly synthesized Gold's reagents were ineffective, thus alternative reaction conditions were examined. Optimization efforts focused on variation of the base employed along with modification of solvent and temperature (Table 1).

When the previously described conditions using NaOMe in MeOH[16a] or NaO-*i*-Pr in *i*-PrOH[15] were employed for the transformation of **1b** to **4c**, modest yields up to 29% were observed (Entries 1 and 2). Alteration of the alkoxide base to NaO-*t*-Bu in *t*-BuOH did not result in product formation (Entry 3). Use of THF as solvent resulted in an improved yield (Entry 4), and it was found that the optimal counterion of the *tert*-butoxide base was lithium (Entry 6), which resulted in formation of the product 4c in 96% yield. Metal amide bases (LiHMDS, NaHMDS, KHMDS, LDA, and LiTMP) were also investigated but led to only modest yields of enaminone **4c.**

2.3. Substrate scope of the formation of enaminones with Gold's reagents

After the reaction conditions for enaminone formation had been optimized with acetophenone, the generality of these conditions was probed by testing the library of Gold's reagents (Scheme 2A).