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Tetrahedron Letters 45 (2004) 8351–8353

Tetrahedron Letters

A simplified green chemistry approach to the Biginelli reaction using 'Grindstone Chemistry'

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Received 18 August 2004; revised 3 September 2004; accepted 8 September 2004
Available online 25 September 2004

Abstract—Grindstone Chemistry—a greatly evolved version of Toda's method of grinding solids together for solvent-free chemical reactions—has been described and its usefulness illustrated by the successful application of this technique to a simplified process for conducting the multi-component Biginelli reaction for the synthesis of physiologically active tetrahydropyrimidinones.

Green chemistry is destined to be a national goal in the near future. In this context, a convenient and rapid synthetic procedure that is energy efficient is highly desirable. To be of practical value, such a procedure should be suitable for large-scale operation also. We wish to describe here a technique with the descriptive title of Grindstone Chemistry that is useful for desktop synthesis as well as kilogram scale operation.

The groundbreaking work of Toda et al. has shown that many reactions (but not all) can be conducted in high yield by just grinding solids together.[1] Usually these reactions were carried out on a very small scale in an agate mortar and pestle. It has been of interest to us to extend this approach to chemical reactions on a large scale without being restricted to interactions between solids only. This modified approach has been given the name of 'Grindstone Chemistry' in our laboratory. We wish to describe here some significant aspects of this type of synthesis that is also suitable for the large-scale preparation of pharmaceuticals and their intermediates.

We have devised techniques for using reagent pairs that may be solid/solid, solid/liquid, or even liquid/liquid. To make the grinding process more efficient it is convenient to add to the reaction mixture some amount of crystalline $MgSO_4 \cdot 7H_2O$, a very common, inexpensive, and water soluble chemical (available even in drug stores). The addition of this friction-enhancing solid has given very satisfactory result in promoting the reaction between liquid reagents by the grinding method. If the reaction products are water soluble, the work-up of the reaction mixture with magnesium sulfate added may be inconvenient. In such a case, sand may be used in place of magnesium sulfate; during work up the sand can be easily removed by filtration.

To conduct Grindstone Chemistry on a large scale a simple and inexpensive expedient is to use a hand held electric food mixer with stainless steel rotors for grinding together the reagents in a large glass or porcelain bowl.

For obtaining a better understanding of the energetics of reactions, a thermocouple connected to a computer was used for recording the 'Reaction Temperature Profile' (change in the reaction temperature with the progression of time) during and after the grinding. Data from several of the successful reactions by grinding described by Tanaka[2] led us to generalize that these reactions are all exothermic. We have concluded that after the reaction is initiated by grinding with the transfer of very small amounts of energy through friction, the reaction proceeds by itself if it is exothermic in nature;

Keywords: Tetrahydropyrimidinone; Reaction by grinding; Solvent-free reaction; *p*-TSA as an acid catalyst.

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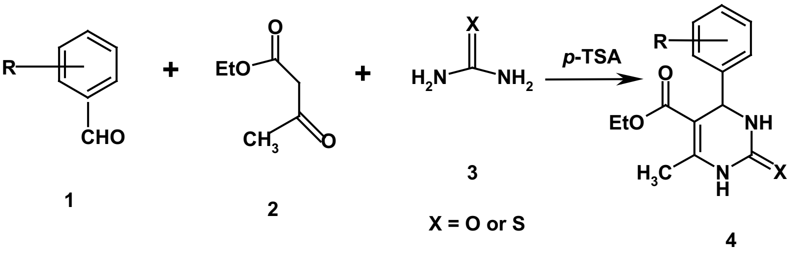
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.09.064

conversely, if the reaction is endothermic, grinding will not make the reaction go forward.

In the course of studies on green chemistry one of our goals has been to redesign conventional and time-honored synthetic methods and make them more eco-friendly and consistent with higher atom economy (i.e., less chemical waste). We have now come to the conclusion that the traditional procedures for many reactions are inefficient and involve unnecessary steps. Heating under reflux for several hours is logical for endothermic reactions. For exothermic reactions, however, such energy input would be superfluous.

The convenience and the time saving that results from the use of Grindstone Chemistry—for small scale as well as large scale reactions—is illustrated here by describing the successful application of this technique to the multi-component Biginelli reaction.

The Biginelli reaction,[3] first described in 1893, has attracted an unprecedented amount of attention in recent years from synthetic and medicinal chemists.[4] Tetrahydropyrimidinones (**4**), prepared by this reaction involving an aldehyde (**1**), a β-keto ester (**2**), and urea (**3**) (or thiourea) and catalyzed by a strong acid have potential use against a number of pathological conditions.



This reaction has been conducted in recent years by heating the reagents or submitting them to microwave irradiation, in presence of a suitable catalyst, in a solvent such as alcohol, glycol, and polyphosphate esters.[5] Many research groups have tried to improve the yield of this reaction by using various acid catalysts such as indium bromide, trifluoroacetic acid, boric acid, potassium hydrogensulfate,[6] zinc chloride,[7] etc.

We wish to report here a simplified and rapid synthetic procedure with high atom economy for the Biginelli reaction. We have found that *p*-toluenesulfonic acid (*p*-TSA), an inexpensive and common organic chemical, is an efficient catalyst for this reaction.

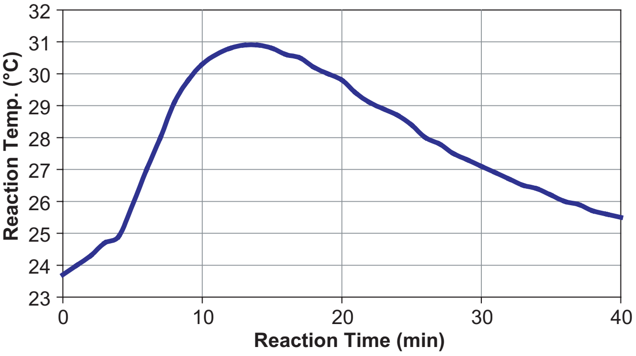


Figure 1. Reaction temperature profile (RTP) of Biginelli reaction using Grindstone Chemistry.

A test experiment was conducted by grinding together equivalent amounts of benzaldehyde, ethyl acetoacetate, urea, and a small amount of *p*-toluenesulfonic acid (as an acid catalyst). Grinding for about 3–5 min led to a light yellow colored solid mass that proved to be mostly the target tetrahydropyrimidinone. The reaction temperature profile as monitored by a thermocouple is shown in Figure 1. It is quite obvious that the Biginelli reaction is exothermic. The crude product was washed with cold water to remove the color; final purification was achieved by crystallization from acetone–EtOH, mp 208–210 °C; yield 94%.

For obtaining larger quantities of the tetrahydropyrimidinone, the reaction was conducted on 0.5 M scale with reagents placed in a large porcelain bowl. Grinding

Table 1. Synthesis of tetrahydropyrimidinone derivatives (**4**) using Grindstone Chemistry

Entry	R	X	Yield (%)	Mp (°C) found	Mp (°C) reported
4a	H	O	93	208–210	209–210[7]
4b	4-OH	O	95	236–238	236–238[7]
4c	4-OCH_3	O	96	208–209[a]	199–201[8]
4d	4-NO_2	O	94	207–208	205–207[8]
4e	4-Cl	O	83	210–211	210–212[9]
4f	H	S	71	205–206	205–206[8]

[a] Melting point of **4c** synthesized by us is higher than that of the corresponding reported.

was conducted with the help of a hand-held electric food mixer with stainless steel rotors. The reaction was complete in less than 15 min. The pale yellow colored product was worked up as before to give 119 g (94% yield), of the desired heterocyclic product. This procedure was used for the efficient preparation of a number of tetrahydropyrimidinones (see Table 1).[10]

This procedure is much simpler and faster than the protocols published to date. It is also consistent with a green chemistry approach since no solvent is needed (except for recrystallization). The catalyst used in an inexpensive chemical that is commonly found in most organic laboratories. Another useful aspect is that this procedure is energy efficient. This reaction can be easily adapted for use as an interesting experiment in an organic chemistry teaching laboratory.

Acknowledgements

We are grateful to the Dreyfus Foundation and the Technogenesis Program of Stevens Institute of Technology for financial support. We thank Hoang Dang,[11] William He,[12] and Jeffery Speck for valuable technical assistance and Prof. F. T. Jones and dean R. Gilman for their encouragement and support.

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10. *Typical procedure for the preparation of tetrahydropyrimidinones*:
    (i) A mixture of an aromatic aldehyde (25 mmol), ethyl acetoacetate (25 mmol), urea (50 mmol), and *p*-TSA (200 mg) was ground for 2–3 min using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidified within 4–15 min. The solid was washed with cold water and recrystallized from ethanol. The yield and mp's are reported in Table 1.
    (ii) The same reactions were also carried out by dissolving urea in minimum amount of water and mixing it with other reactants (in the same proportions as mentioned above). The mixture was then ground for 2–3 min by adding 1 g of sand. The mixture solidified within 5–15 min giving clean white product that was washed with water and crystallized from ethanol when sand was also removed at the same time. The yields of the products were the same as obtained by the above method.
    (iii) The large scale preparation of **4a** was carried out by grinding benzaldehyde (1.06 kg, 10 mol), ethyl acetoacetate (1.30 kg, 10 mol), urea (1.20 kg, 20 mol) and *p*-TSA (80 g) for 3 min using kitchen Aid Mixture. The usual work up of the reaction as stated above gave **4a** with 93% yield.All the products were characterized by ^1H NMR spectroscopy and by comparison of their physical characteristics with those of the authentic samples.
11. Undergraduate participant in the Technogenesis program of Stevens Institute of Technology.
12. Undergraduate participant in the MERCK–SURF program of Merck Company.