

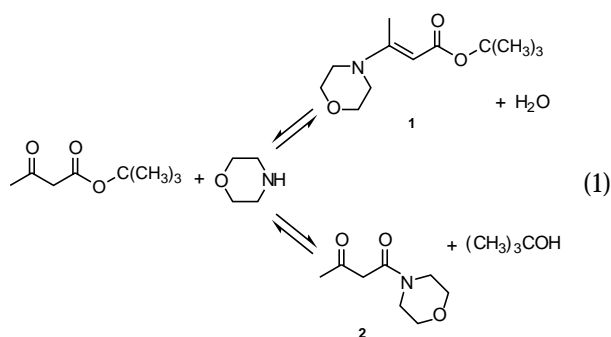
# Reaction of Morpholine with *t*-Butyl Acetoacetate: A Study in Kinetic vs Thermodynamic Control, Product Identification, and Molecular Modeling

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There are only a limited number of experiments that a student can do each semester in an undergraduate organic chemistry course. Therefore, it is important for each experiment to illustrate as many different techniques and principles as possible. The experiment discussed in this article demonstrates the following principles and techniques: (i) kinetic versus thermodynamic control of a reaction, (ii) methods to be used and pitfalls to be avoided in identification of reaction products, (iii) use of molecular modeling for identification of the thermodynamically controlled reaction product.

The reaction of morpholine with *t*-butyl acetoacetate in a one-to-one molar ratio results in one of two products, enamine ester **1** or ketoamide **2** (eq 1). The reaction of a secondary amine with an acetoacetic ester to form an enaminoester is well known (1–3). The *t*-butyl ester was used in our experiment instead of the more common ethyl ester because *t*-butyl morpholine enamine **1** (4) is a solid that melts well above room temperature. The corresponding ethyl enaminoester possesses a melting point very near to room temperature (5) and is therefore difficult to crystallize. The reaction of a secondary amine with an acetoacetic ester to form a ketoamide has been reported (5, 6). It has been demonstrated that the enaminoester is the kinetically controlled product and the ketoester is the thermodynamically controlled product (7).



These reactions provide the basis for an experiment in which the competition between thermodynamic control and kinetic control takes place between two functional groups on a single molecule competing for a single reagent. This is in contrast to a traditional experiment used to demonstrate this principle, which is found in many organic laboratory manuals (8). In that experiment two different molecules (cyclohexanone and 2-furaldehyde) compete for a single reagent (semicarbazide).

During a discussion of the reaction, the students are informed of the identities of the two possible products. Conditions under which one might expect kinetic control of a reaction product as contrasted with conditions for thermodynamic control are discussed.

## Experimental Procedure

Students place a mixture consisting of a 1:1 molar ratio of morpholine and *t*-butyl acetoacetate into a beaker cooled with ice water. A very few molecular sieve pellets (3A, 4–8 mesh) are put into the beaker (two pellets for 0.05 mol works well). The beaker is covered with a watch glass and placed in the student's drawer or some other secure area for study the following laboratory period, when it will be observed that crystals have formed in the beaker.

Some *t*-butyl acetoacetate (0.05 mol works well here, as it did for enamine formation) is placed in a flask equipped with a magnetic stirring bar, an addition funnel, and a distillation adapter leading to a condenser. The flask is heated to 165 °C (either with a silicone oil bath or a heating mantle). Then an equimolar amount of morpholine is slowly added while the temperature is maintained between 165 and 175 °C. During the slow addition of morpholine, some liquid (*t*-butanol) distills over. After the morpholine addition is complete, the liquid continues to distill. When the distillation of the lower-boiling liquid is complete, the reaction mixture is allowed to cool and is then transferred to a beaker. The beaker is covered with a watch glass and placed in the student's drawer or a secure area. Colorless crystals will have formed in the beaker by the next laboratory period. Microwave irradiation of a Teflon-coated reaction vessel containing this equimolar reaction mixture using a microwave oven is another method for carrying out this higher-temperature reaction. This results in a much shorter reaction time, but it is harder to control the reaction conditions using this method.

During the following laboratory period the molecular sieves are mechanically removed from the crystals of the first (lower-temperature) beaker. The crystals are isolated by vacuum filtration, washed with a small amount of ether, and allowed to dry. The crystals from the second (higher-temperature) beaker are also isolated by vacuum filtration, washed with ether, and allowed to dry.

## Results and Discussion

The solid product from the room-temperature reaction is enaminoester **1**; the crystals from the higher-temperature reaction are ketoamide **2**. However, identification of these products is not straightforward. The melting point of enamine ester **1** is 70–72 °C, and the melting point of ketoamide **2** is 69–71 °C. (The amide may be recrystallized from toluene, but it isn't necessary.) The obvious conclusion from the nearly identical melting points of the two crystalline solids is that they are identical, and the same product is both the kinetically controlled and the thermodynamically controlled reaction product.

Table 1. Mass Spectra

Enaminoester 1			Ketoamide 2		
<i>m/z</i>	Rel. Abundance	Fragment Lost	<i>m/z</i>	Rel. Abundance	Fragment Lost
227	13	parent	171	34	parent
170	39	C(CH <sub>3</sub> ) <sub>3</sub>	128	49	COCH <sub>3</sub>
154	34	OC(CH <sub>3</sub> ) <sub>3</sub>	86	100	COCH <sub>2</sub> COCH <sub>3</sub>
126	100	OCOC(CH <sub>3</sub> ) <sub>3</sub>	57	86	morpholineCO

However, further investigation of the two reaction products show this not to be the case. A mixture melting point of the two crystalline reaction products shows both a depressed melting point and a broadening of the melting point range. A mass spectrum of the room-temperature crystals shows them to be enaminoester 1 (see Table 1). The mass spectrum of the crystalline product obtained from the higher-temperature reaction shows this to be ketoamide 2 (Table 1). Both proton and carbon magnetic resonance spectra of each set of crystals show the room-temperature crystals to be enaminoester 1 and the high-temperature crystals to be ketoamide 2 (Table 2). DEPT spectra help to confirm the carbon spectral assignments. Use of carbon NMR prediction software such as Softshell's C-13 NMR Module is very useful here. The HETCOR 2-D NMR spectra aid in the proton spectral assignments, but obtaining these spectra is very time consuming for the student and not necessary for the analysis. Students can determine the amount of enol form of ketoamide 2 present in deuteriochloroform by integrating the proton magnetic resonance signals of the amide's terminal methyl group signals at 1.95 (enol) and 2.27 (keto) ppm. This shows that there is about

Table 2. NMR Spectral Shifts

Iso- tope	$\delta$ /ppm							
	1	2	3	4	5	6	7	8
	$t\text{-Butyl Acetoacetate}$							
<sup>13</sup> C	29.6	200.6	51.0	166.0	81.4	27.6	—	—
<sup>1</sup> H	2.25(s)	—	3.36(s)	—	—	1.48(s)	—	—
	$\text{Enaminoester 1}$							
<sup>13</sup> C	14.8	160.1	90.3	168.3	77.7	28.2	46.1	66.1
<sup>1</sup> H	2.37(s)	—	4.74(s)	—	—	1.15(s)	3.18(t)	3.71(t)
	$\text{Ketoamide 2}$							
<sup>13</sup> C	29.6	201.6	48.7	164.6	—	—	41.3	65.8
<sup>1</sup> H	2.27(s)	—	3.58(s)	—	—	—	3.65	3.67
	$\text{Enolamide 2}$							
<sup>13</sup> C	21.7	174.7	85.6	170.1	—	—	46.0	65.9
<sup>1</sup> H	1.95(s)	—	5.15(s)	—	—	—	3.41 <sup>a</sup>	3.67

<sup>a</sup>This assignment is based on HETCOR 2-D NMR and differs from the assignment made by Torosyan, et al. (7).

Table 3. Molecular Modeling Calculations

Compound	Semiempirical AM-1/ kcal mol <sup>-1</sup>	Ab initio 6-31G*/ hartrees
Water	-59.240	-76.0107465
<i>t</i> -Butanol	-71.601	-232.1534707
Morpholine	-49.346	-285.9977181
<i>t</i> -Butyl acetoacetate	-142.548	-535.7136091
( <i>Z</i> )-Enamine 1	-121.131	-745.6603501
( <i>E</i> )-Enamine 1	-123.018	-745.6688848
Ketoamide 2	-118.092	-589.5542168
( <i>Z</i> )-Enolamide 2	-116.511	-589.5481199

15% of the enol form and 85% of the keto form present in the fairly polar deuteriochloroform solvent. The IR spectrum (Nujol mull) of enaminoester 1 shows bands at 1699 and 1597 cm<sup>-1</sup>. The IR spectrum (Nujol mull) of ketoamide 2 shows bands at 1723 and 1640 cm<sup>-1</sup>.

The students can determine which reaction is thermodynamically favored (at least in the gas phase) according to theoretical semiempirical molecular modeling calculations. AM-1 calculations using a molecular modeling program such as Spartan show the reaction resulting in the formation of ketoamide 2 to be the favored reaction by about 7.5 kcal/mol; that is for enaminoester 1, -59.240 - 123.018 = -182.258 kcal/mol, and for ketoamide 2, -118.092 - 71.601 = -189.693 kcal/mol (see Table 3). Ab initio calculations using HF/6-31G\* give a similar result of 0.0280572 hartree (ignoring zero-point energies), favoring ketoamide 2. In these calculations the more stable keto form of ketoamide 2 is used, and the more stable *E* isomer of enaminoester 1 is used.

An additional module may be added to this experiment. A very small amount of a solution cooled to ice-bath temperature of a 1:1 molar ratio of morpholine and *t*-butyl acetoacetate is injected into a GC-MS, and a chromatogram and some mass spectra are obtained. The column is an SE-30 capillary column, and the GC is programmed to start at 70 °C and reach a maximum temperature of 230 °C over a period of about 6 minutes. Analysis of this chromatogram shows about 98% ketoamide 2 and 2% enaminoester 1. The ketoamide has a shorter retention time than the enaminoester, identification of the peaks being obtained from the mass spectra. This chromatogram indicates almost exclusively ketoamide 2 as the product at this low temperature and hence it "appears" to be the kinetically controlled product, which is contrary to the actual fact. This is a good illustration of the possibility (and in this case, the actuality) of reactions taking place on a GC column. Indeed, it has been shown by an "on-column pursuit" experiment that this reaction does take place in a column at 190 °C, with  $\beta$ -keto esters forming ketoamides on the GC column when they are allowed to react with secondary amines (9). The students can demonstrate the on-column pursuit technique with this reaction by first injecting the less volatile  $\beta$ -ketoester onto the column and then injecting the more volatile amine to produce a significant  $\beta$ -ketoamide peak.

The whole experiment can take as little as part of one period and one-half of a subsequent period or as much as two periods, depending upon the extent of the spectral part of the product identification.

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