ChemInform Abstract: Chemistry and Reactivity of α-Substituted Ketones in Isonitrile-Based Multicomponent Reactions

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Studies on the Chemistry and Reactivity of α-Substituted Ketones in Isonitrile-Based Multicomponent Reactions

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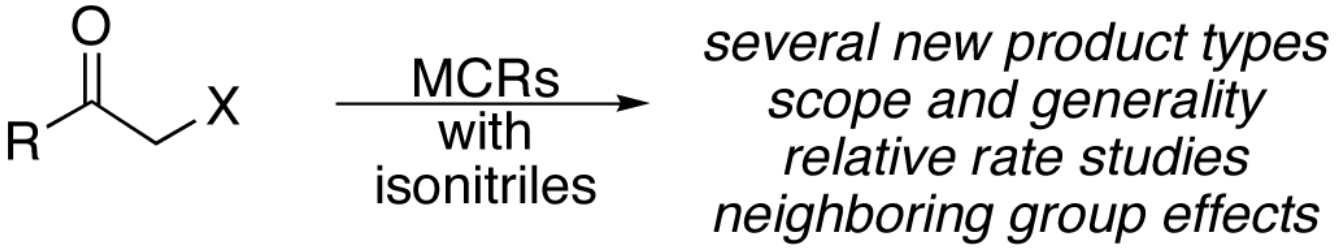
Abstract



Using the Passerini and Ugi reactions as representative tests, the utility of several α-substituted ketones R-CO-CH_2-X (X= sulfonyloxy, acyloxy, azido, halo, hydroxy and sulfonyl) in isonitrile-based multicomponent reactions was explored. In a relative rate study (R= $PhCH_2CH_2$), each of the α-substituted ketones underwent Passerini condensation more rapidly than the parent ketone. Short, highly convergent routes to oxazoline, β-lactam, di-O-acylglyceramides, and other molecular frameworks were developed.

Keywords

Multicomponent Reactions; Diversity-Oriented Synthesis; Synthetic Methodology

INTRODUCTION

The discovery in 1850 that α-amino acids could be prepared in one step from simple reactants using the Strecker reaction, the first reported example of a multicomponent reaction (MCR), launched a period of intensive synthetic chemical development that remains active today. Generally defined as one-pot processes that produce a desired target from the combination of three or more reactants,[1] MCRs can create simple and convergent paths to structurally complex products in atom-economical[2] fashion. With the advent of combinatorial chemistry and its widespread adoption by the pharmaceutical industry, MCR chemistry experienced a renaissance of interest in the past two decades, triggered initially by the demand for screening libraries in drug discovery programs, and stimulated more recently by efforts to assemble natural product-like scaffolds exhibiting specific pharmacological profiles.

To date, MCR reactions based on the chemistry of isonitriles have been particularly widely used in these endeavors, despite the well-known drawbacks to using this family of compounds.

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[1]Dedicated to the memory of the late Professor A. I. Meyers

Besides their unpleasant olefactory properties, isonitriles have generally been limited in their commercial availability and have limited shelf stability. In recent years, however, versatile new syntheses of isonitriles have been developed,[3] including routes to convertible isonitriles possessing pleasant aromas,[4] that promise to expand the repertoire of known MCRs.

The Passerini and Ugi reactions, which represent the two most widely-employed isonitrile-based MCRs, also need simple carbonyl compounds as integral reactants. As part of our efforts to synthesize new molecular frameworks by using the "single reactant replacement" (SRR) strategy to evolve existing MCRs, we have investigated aldehydes and ketone surrogates that combine carbonyl electrophilic properties with additional embedded reactivity elements. For example, we recently discovered that replacing simple carbonyl compounds in the Passerini reaction with acyl cyanides made it possible to redirect the outcome to afford β-aminoacid diamides instead of the conventional α-acyloxyamides,[5] and further empowered the assembly of densely-functionalized oxazoles and tetrazoles.[6]

We also investigated the use of α-diazoketones in isonitrile-based MCRs, finding them resistant to Passerini and Ugi reactions. However, by exploiting the reactivity of diazocarbonyls to Bronsted acids or transition metal catalysis, we recently achieved successful one-pot, four-component condensations that furnished substituted oxazolines via α-sulfonyloxyketones[7] as well as substituted di-O-acylglyceramides from α-acyloxyketones.[8] Following those communications, we now report a full account of our studies using α-substituted ketones as surrogates for simple carbonyl compounds in the Ugi and Passerini reactions.

The rationale for this study was to investigate SRR outcomes when reactive functionality was embedded at the α-position of the ketone. While several reactive α-substituents were of potential interest (sulfonyloxy, acyloxy, azido, halo, hydroxy and sulfonyl), almost nothing was known about their MCR chemistry, let alone relative reactivities. Prior to our own oxazoline-forming synthesis, there were no reports of Passerini or Ugi condensations on α-mesyloxy- or tosyloxyketones. Likewise, no examples of MCRs of α-azido-, α-hydroxy-, or α-sulfonylketones have been described in the literature. Enantioselective, copper-catalyzed Passerini reactions of alkoxy-substituted aldehydes have recently been described,[9] but no examples of the corresponding alkoxyketones were included. Alpha-chloroketones have been reported to undergo the Passerini condensation, forming chloro-substituted acyloxyamides, which after subsequent base treatment were transformed into the corresponding acyloxy-β-lactams.[10]

It occurred to us that any pronounced rate differences between these various substituted ketones might make it possible to achieve selectivity when using mixtures of two or more carbonyl compounds, thus broadening the opportunities for incorporating novel functionality in MCRs. Anchimeric effects involving the neighboring α-substituent might also be exploited to produce new molecular frameworks. Here we report the relative rates of condensation of a representative series of α-substituted ketones in the Passerini condensation. That kinetic study provides useful new insights into the relative reactivity of each family and suggests additional directions for new work.

RESULTS AND DISCUSSION

Preparation of Substrates

The starting material for all α-substituted ketones was the corresponding α-diazoketone **1** (Scheme 1), which could be conveniently prepared by reaction of the cognate acid chloride with diazomethane. Initially, the readily available 1-diazo-4-phenyl-2-butanone **1a** (prepared from hydrocinnamoyl chloride) was used to synthesize a representative example of each family of substituted ketones. Reaction of **1a** with methanesulfonic acid or toluenesulfonic acid

furnished the mesyloxy and tosyloxyketones **2a** and **3a**, respectively.[11] The corresponding acyloxyketone **4a** (R^2=CH_3) was prepared from **1a** by $Cu(acac)_2$-catalyzed reaction with acetic acid.[12] Chloroketone **5a** was obtained from **1a** by reaction with HCl in ether.[13]

Azidoketones **6** and arylsulfonylketones **7** were both prepared according to literature methods from the corresponding chloroketones **5**. Thus, azidoketone **6a** arose from the reaction of **5a** with NaN_3 in DMF.[14] The synthesis of α-sulfonylketone **7a** (Ar = Ph) was achieved by reaction of **5a** with thiophenol and NaOH in the presence of oxone.[15] A sample of the parent unsubstituted ketone, benzylacetone **8a**, was obtained commercially and used as a control compound for the kinetic study.

Relative Rate Study of α-Substituted Ketones in the Passerini Reaction

Compounds **2a** and **4a**-**8a** were subjected to a representative Passerini condensation with acetic acid and *t*-butyl isonitrile (1.0 equiv each) under neat conditions at rt. Aliquots of each reaction mixture were removed for NMR analysis, and the progress of the reaction was monitored by the relative amounts of starting ketone (as judged by integration of the singlet resonance for the α-methylene carbon) and the Passerini product (as measured by the AB-quartet for the same methylene group). The results are tabulated in Figure 1.

As the data indicate, each of the α-substituted ketones underwent Passerini condensation more rapidly than the parent carbonyl compound **8a**. Mesyloxyketone **2a** was the most reactive carbonyl compound tested. Although tosylate **3a** was not included in the rate study, independent side-by-side comparisons of **2a** and **3a** in other Passerini and Ugi condensations (*vide infra*) established that **3a** displayed comparable reactivity in isonitrile-based MCRs. Chloroketone **5a** and azidoketone **6a** showed similar rate profiles, and were somewhat more reactive than acyloxyketone **4a**. Sulfonylketone **7a** was the least reactive of the substituted ketones tested, undergoing Passerini condensation only slightly faster than **8a**. The kinetic data in Figure 1 were consistent with the expected enhancement of carbonyl electrophilicity caused by electronegative substituents, as judged by known Pauling atom or group electronegativity values for each of the substituents tested.[16]

Results with compounds **2a**, **5a**, and **6a** suggested that selective Passerini condensations on these substances might be possible in the presence of a sulfonyl-substituted or unsubstituted ketone. As a preliminary test of this hypothesis, a 1:1 mixture of chloroacetone **5b** (R^1= CH_3) and phenylsulfonylacetone **7b** (R^1= CH_3) were reacted with 1 equiv each of acetic acid and *t*-butyl isonitrile (24 h, rt) to afford an 8:1 ratio of products from **5b** and **7b**, respectively.

Isonitrile-Based MCRs of Substituted Ketones

Mesyloxy and tosyloxyketones **2** and **3** proved to be very good carbonyl components in the Passerini reaction, typically forming the expected products **9** and **10**, respectively, in high yields (Scheme 2).

The results of a representative sampling of condensations using various carboxylic acids and isonitriles (1.1 equiv each) are summarized in Table 1.

Condensations of **2** and **3** were generally completed in 12-18 hours and successfully furnished the expected products in very good to excellent yields. Products **9** and **10** were readily purified by flash column chromatography. Furthermore, the possibility of directly converting the parent α-diazoketone to mesylate **9a** was realized in a simple one-pot process by reacting a CH_2Cl_2 solution of diazoketone **1a** with methanesulfonic acid (1.1 equiv, 10 min, 0 °C). After addition of NaOAc (0.5 equiv) to neutralize residual acid, the solution was treated with acetic acid and cyclohexyl isonitrile (rt 24 h) to afford **9a** in 86% yield.

With their reactive sulfonate leaving groups, sulfonates **9** and **10** were also well-suited precursors for the synthesis of substituted β-lactams **11** (Scheme 3) following a procedure developed for cyclizations of the corresponding chloro compounds.[10]

Table 2 summarizes results obtained in our lab using this approach to substituted β-lactams from representative sulfonates **9** and **10**. While the yields of **11a-e** were generally comparable whether from the mesylate or tosylate precursor, the cyclization was noticeably more rapid in the case of mesylate **9c**.

We also investigated Ugi reactions of sulfonyloxyketones **2** and **3**. When using ammonia as the amine, the MCR led to a novel 4-component synthesis of substituted 2-oxazolines **13** (Scheme 4) by way of the intermediate diamides **12**.[7] Apparently the formation of imines derived from **2** or **3** was faster than ammonolysis of the mesylate or tosylate group, thus triggering the desired Ugi reaction to form **12**. The fact that **12** cyclized spontaneously to **13** during the reaction finds precedent in the known biosynthesis of peptide-based oxazolines[17] by cyclization of activated N-acylserine derivatives.[18]

Initial studies of this interesting transformation with **2a** as a representative mesyloxyketone utilized methanol as solvent, a common medium for Ugi condensations, and also afforded significant quantities of the corresponding Passerini product **9**. This byproduct could be effectively suppressed by replacing methanol with 2,2,2-trifluoroethanol, a solvent that was recently reported to improve Ugi reactions involving ammonia as the amine component.[19] Overall, the new oxazoline synthesis, for which full experimental details on 14 examples have been reported,[7] accommodated a broad range of sulfonyloxyketones, isonitriles and carboxylic acids.

Our initial communication noted that when NH_3 was replaced with benzylamine, the MCR of **2a** with acetic acid and cyclohexyl isonitrile afforded aminoester **15a** (Scheme 5) as the exclusive product. Particularly characteristic was the strong ester carbonyl band (1740 cm^{-1}) in the IR spectrum of **15a**.

A mechanism of formation of **15a** paralleling that of **13** could be envisioned in which hydrolysis of the oxazolinium intermediate **14a** led to the observed product. Interestingly, **15a** did not undergo 1,2-acyl shift, leading to the corresponding amidoalcohol **16a**. Further confirmation of the structure of **15a** was obtained by single crystal x-ray diffraction analysis.

Structures such as **16a** embody the hydroxyethylene or hydroxyethyl structural unit found in transition state isosteres such as statine or norstatine, which have been developed as inhibitors of retroviral proteases.[20] Given their potential biomedical significance, we have investigated this MCR further. As indicated in Table 3, several other primary amines and mesyloxyketones formed the corresponding amidoesters **15**. In each case, only the amidoester isomer **15** (and none of the diamide **16**) was detected.

To determine whether the products observed in each case were formed under kinetic control, aminoester **15a** was subjected to basic (DBU-CH_3CN, Et_3N, NaH-DMF) equilibration conditions. However, no evidence for the formation of diamide **16a** was obtained from these experiments.

The complementary equilibration experiment required an authentic sample of **16a**, which we attempted to synthesize from acetoxyketone **4a** in two steps using the Ugi reaction as shown below (Scheme 6). Little is known about Ugi condensations of such acyloxyketones. In fact, reaction of **4a** with ammonia, acetic acid, and cyclohexyl isonitrile returned mostly starting ketoacetate **4a**, along with the corresponding Passerini product (not shown) in 14% yield.

However, replacing ammonia with benzylamine did afford the desired MCR product **17a** in 67% yield.

Treatment of **17a** with NH_3-CH_3OH was expected to furnish **16a** by methanolysis of the more reactive acetate ester. Instead, two products were formed: aminoester **15a** (20%) and aminoalcohol **18a** (60% yield). Unfortunately, none of the hoped-for amidoalcohol **16a** could be detected by IR.

In an alternative approach (Scheme 7), the known[21] hydroxyketone **19** was subjected to the Ugi reaction with benzylamine, acetic acid and cyclohexyl isonitrile. Instead of the expected amidoalcohol **16a**, the sole product of that reaction (56%) was aminoester **15a**. Taken together, the results depicted in Schemes 6 and 7, while not conclusive, were consistent with the rapid conversion of **16a** to **15a** and its hydrolysis product **18a**.

It became apparent from efforts to prepare **16a** that Ugi condensations of acyloxyketones **4**, while feasible, suffered certain limitations. Therefore, we decided to study the reactivity of acyloxyketones in the corresponding Passerini reactions. A recently published preliminary report summarized our findings in this area.[8] Since acyloxyketones of general structure **4** were easily prepared by copper-catalyzed insertion of diazoketone **1** into a carboxylic acid,[22] we were able to develop a versatile one-pot 4-component condensation in two stages leading to a new family of structurally diverse di-O-acylglyceric acid amides **20** (Scheme 8).

The initial insertion stage required heating of **1** with R^2CO_2H (30-60 min, toluene, 60-90 °C), usually in the presence of 1.0 mole-% $Cu(acac)_2$. Once gas evolution ceased, the toluene was removed in vacuo and the crude acyloxyketone **4** was subjected to a Passerini condensation with R^3NC and R^4CO_2H. Table 4 summarizes the range of new glyceramide diesters that could be synthesized using this method.

One advantage of the method over stepwise acylation of the *vic*-diol moiety in glyceramides is that it avoids the potential for ester interchange by competing O,O-acyl transfer side reactions. Moreover, by using one hydrophobic and one hydrophilic carboxylic acid (e.g. **20i**), the approach depicted in Scheme 8 can be used to synthesize facially amphiphilic glyceramides for potential biomedical use, whether as cell-wall disrupting agents displaying antifungal activity or as encapsulating agents in micellar drug delivery. The method can be adapted to introduce different chain lengths in each ester group to fine-tune desired hydrophobic/hydrophilic properties.

The use of α-chloroketones **5** in isonitrile-based multicomponent reactions was also of interest in this investigation. Since Passerini reactions of **5** have already been described,[10] we turned our attention to Ugi 4-component condensations of chloroacetone **5b** (R= CH_3) as a representative chloroketone using conditions optimized for the corresponding mesyloxyketones **2**. Thus, reaction of **5b** with ammonium acetate (4 equiv) and t-butyl isonitrile (1.1 equiv, rt, 24 h) in trifluoroethanol solvent afforded the normal Ugi product **21a** in very good yield. Likewise, condensation of **2b** with NH_4OAc and cyclohexyl isonitrile also afforded the expected Ugi product **21b**, along with small quantities of the corresponding Passerini product **22**.

Using benzylamine instead of ammonia, the Ugi condensation of **5b** took a different path, forming aminoester **15f** (Scheme 10) in 74% yield, along with a small amount of the corresponding Passerini product (14%, structure not shown). As depicted in Scheme 10, the formation of aminoester **15f** likely proceeded by an initial Ugi reaction leading to **23**, followed by a rearrangement via **14f** similar to that invoked for related structures **15a-e** (Scheme 5).

Chloroketone-derived Ugi products like **21a** and **21b** would be particularly useful if they underwent cyclization to the corresponding acylamino-β-lactams **24** (Scheme 11), which embody the key structural element of penicillins, cephalosporins, and other β-lactam antibiotics at the forefront of modern antimicrobial chemotherapy.[23] Not surprisingly, however, exposure of **21a** to mild base instead formed the known[17] oxazoline **13a**.

We reasoned that replacing the acetamide group in **21a** with a phthalimide would block the undesired formation of an oxazoline. Moreover, if the Ugi condensation of **5b** using phthalic acid in combination with ammonia and *t*-butylisonitrile were successful, the initally-formed phthalimidic acid **25** (Scheme 12) might spontaneously dehydrate to the phthalimide **26** either during workup or upon standing, thus paving an approach to the desired β-lactam **27**.

After testing the solubility of ammonium phthalate in various solvents, we chose methanol as the solvent for the Ugi reaction depicted in Scheme 11. Chloroketone **5b** was added to a suspension of ammonium phthalate (4 equiv, 0 °C, 10 min), followed by *t*-butyl isonitrile (1.1 equiv, rt. 16 h). Extractive workup afforded acylaziridine **28** (Scheme 13) in 33% yield. However, when the Ugi reaction was repeated using the less nucleophilic trifluoroethanol as solvent, only traces of phthalimide **26** were detected by mass spectrometry. Instead, the major product was hydroxyamide **29**, apparently the result of a 2-component Passerini condensation. The structure of **29** was confirmed by single crystal x-ray analysis (Figure 2).

The relatively rapid Passerini reaction of **6a** (Figure 1) suggested that such azidoketones, although heretofore unstudied in isonitrile-based MCRs, would be good substrates for such complexity-generating processes. Furthermore, alkyl azides are particularly useful components in the synthesis of triazoles and tetrazoles by copper-catalyzed cycloadditions with alkynes using “click” chemistry.[24] As shown in Scheme 14, representative Ugi condensations of **6a** and **6d** (R= CH_3) with ammonium acetate and *t*-butyl isonitrile afforded the expected diamides **30** and **31** (Scheme 14) in reasonable yield.

We also investigated isonitrile-based MCRs of α-arylsulfonylketones having general structure **7**. Unlike other representative α-substituted ketones in this study, sulfonylketones (also known as β-ketosulfones) are distinguished by their relatively acidic methylene hydrogens and have widespread applications, in the synthesis of disubstituted alkynes,[25] alkenes,[26] allenes,[27] and heterocycles.[28] Some β-ketosulfones function as aromatase inhibitors[29] and also exhibit fungicidal activity.[30]

The Passerini condensation of phenylsulfonyl ketone **7a** (Scheme 15) with acetic acid and *t*-butyl isonitrile (1 equiv each) reported in the kinetic study (Figure 1) proceeded smoothly (rt, 1 d) to afford the expected product **32a** (46% yield) as an inseparable 1:1 mixture with **7a**, based on NMR analysis.

The process seemed to be general, judging from the representative cases shown in Table 5, in which variations to the arylsulfonyl group and to the carbon framework of the ketone were introduced. Unlike **32a**, products **32b-f** were obtained pure after flash chromatography. Interestingly, using 2 equiv of acid and isonitrile shortened the overall reaction time, but failed to improve the yield of product.

A representative Ugi condensation using phenylsulfonyl ketone **7b** with ammonium acetate and *t*-butyl isonitrile was performed as an initial reactivity test, and afforded the expected product **33a** (Scheme 16, 54%). However, additional examples summarized in Table 6 defined a narrow scope of reactivity.

In entry 2, the low yield obtained of product **33b** could not be improved by switching the solvent to the more commonly used methanol, and was apparently due to the poor solubility

of benzoic acid in either solvent. Attempts to use benzylamine in place of ammonia produced complex mixtures in which neither the Ugi (expected) nor Passerini product could be identified. Generally, the reaction was successful with a number of isonitriles including *t*-butyl or *n*-butyl isonitrile as well as ethyl isocyanoacetate.

CONCLUSION

In conclusion, we have shown that numerous α-functionalized ketones having general structures **2**-**7** can serve as useful carbonyl components in isonitrile-based MCRs, occasionally with unexpected and surprising outcomes. The successful application of Passerini and Ugi condensations to families of ketones **2**-**7** enhances the utility of these two powerful name reactions, and adds another dimension to the structural complexity that can be achieved using multicomponent reactions.

EXPERIMENTAL SECTION

Representative procedure for the Passerini reaction of α-mesyloxyketones 2

Compound 9a—To a sample of α-mesyloxyketone **2a** (48 mg, 0.2 mmol) under N_2 in a 5 mL roundbottom flask was added acetic acid (13 μL, 0.22 mmol, 1.1 equiv) and *t*-butyl isonitrile (25 μL, 0.22 mmol, 1.1 equiv). The resulting homogeneous solution was stirred at rt under N_2 for 20 h. The product was purified by silica gel flash column chromatography (3:7 EtOAc:hexanes, R_f= 0.2) to afford **9a** (68 mg, 88%) as a pale yellow oil.

Representative procedure for the synthesis of acyloxy-β-lactams

Compound 11a—To a suspension of freshly washed (pentane) sodium hydride (9 mg of 80% dispersion, 0.3 mmol, 1.5 equiv) in 4:1 CH_2Cl_2:DMF (3 mL) in a dry 25 mL roundbottom flask under N_2 at 0 °C was added a solution of **9c** (82 mg, 0.2 mmol) in 4:1 CH_2Cl_2:DMF (3 mL) dropwise. The reaction mixture was stirred at rt for 2 h. Saturated NH_4Cl (6 mL) was then added and the mixture stirred for 30 min at rt. After separating the layers, the aqueous phase was extracted with CH_2Cl_2 (5 mL) and the combined organic layers were washed with H_2O (5 mL) and saturated NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate:hexanes, R_f= 0.3) to afford the desired product **11a** as a pale yellow oil.

Representative procedure for the Ugi reaction of α-mesyloxyketones 2 with primary amines

Compound 15a—To a solution of α-mesyloxyketone **2a** (48 mg, 0.2 mmol, 1 equiv) in anhydrous 2,2,2-trifluoroethanol (0.5 mL) at 0 °C was added benzylamine (178 μL, 0.8 mmol, 4.0 equiv) dropwise. The reaction mixture was stirred for 10 min at 0 °C, then acetic acid (23 μL, 0.4 mmol, 2.0 equiv) and cyclohexyl isonitrile (27 μL, 0.22 mmol, 1.1 equiv) were added via syringe with stirring. The reaction mixture was then warmed to rt and stirred for 18 h. After removing the solvent *in vacuo*, the residual oil was purified by silica gel flash column chromatography (3:7 ethyl acetate:hexanes, R_f= 0.3) to afford **15a** as a white solid (57 mg, 71%).

Representative procedure for the synthesis of di-O-acylglyceramides

Compound 20b—A mixture of acetic acid (57 μL, 1.0 mmol) and $Cu(acac)_2$ (2.6 mg, 0.01 mmol, 1 mol %) toluene (2 mL) in a 10 mL roundbottom flask was heated to 60 °C for 10 min under nitrogen. To it was added dropwise a solution of diazoketone **1a** (226 mg, 1.3 mmol, 1.3 equiv) in toluene (2 mL). Once gas evolution was judged complete, the reaction mixture was stirred an additional 5 min, then cooled and concentrated *in vacuo*. The oily residue was blanketed in nitrogen, then treated with *iso*-butyric acid (140 μL, 1.5 mmol, 1.5 equiv) and *t*-

BuNC (170 μL, 1.5 mmol, 1.5 equiv). The resulting reaction mixture was stirred at rt under N_2 for 20 h. The product was purified by silica gel flash column chromatography (1:1 EtOAc:hexanes, R_f= 0.3) to afford **5b** (338 mg, 90%) as a pale yellow oil.

Representative procedure for the Passerini reaction of α-sulfonylketones 7

Compound 32d—To a stirred solution under N_2 of freshly dried phenylsulfonylacetone **7b** (67 mg, 0.34 mmol) in CH_2Cl_2 (0.02 mL, 19 *M*) was added isobutyric acid (37 μL, 0.37 mmol) followed by cyclohexylisonitrile (45.5 μL, 0.37 mmol). The reaction mixture was stirred at rt for four days, then volatile residues were removed under reduced pressure. After TLC analysis,[31] the product was purified by silica gel flash chromatography (2:1 ethyl acetate:hexanes, R_f = 0.5) to furnish pure **32d** (92 mg, 69%) as a colorless oil.

Representative procedure for the Ugi reaction of α-sulfonylketones 7

Compound 33a—A solution of NH_4OAc (101 mg, 1.31 mmol) and freshly dried phenylsulfonylacetone **7b** (65 mg, 0.33 mmol) in anhydrous 2,2,2-trifluoroethanol (add vol, 0.4 *M*) under N_2 was stirred at 0°C for 1 h. The, *t*-butyl isonitrile (41 μL, 0.36 mmol) was added and stirring at rt was continued for two days. Volatiles were removed under reduced pressure, and after TLC analysis,[31] the crude oily product was purified by silica gel flash chromatography (10:1 ethyl acetate: hexanes, R_f 0.3) to furnish pure **33a** (60 mg, 54% yield) as a white solid (mp 175-176 °C).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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31. In cases where the product had the same R_f value as the starting ketone, the crude product was dissolved in CH_2Cl_2 and washed with 0.2 *M* NaOH saturated with NaCl. The aqueous layer was back-extracted twice with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated prior to chromatography.

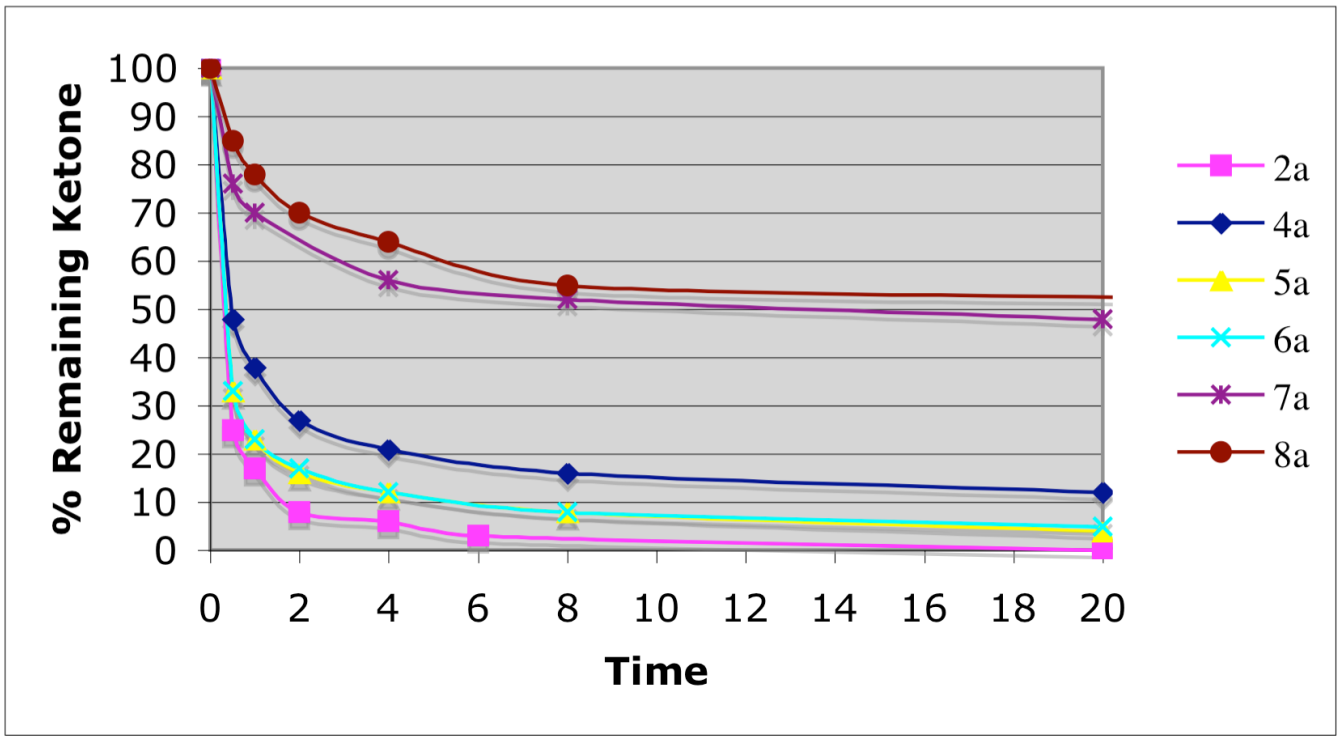


Figure 1.
Relative rates of a prepresentative Passerini condensation of α-substituted ketones

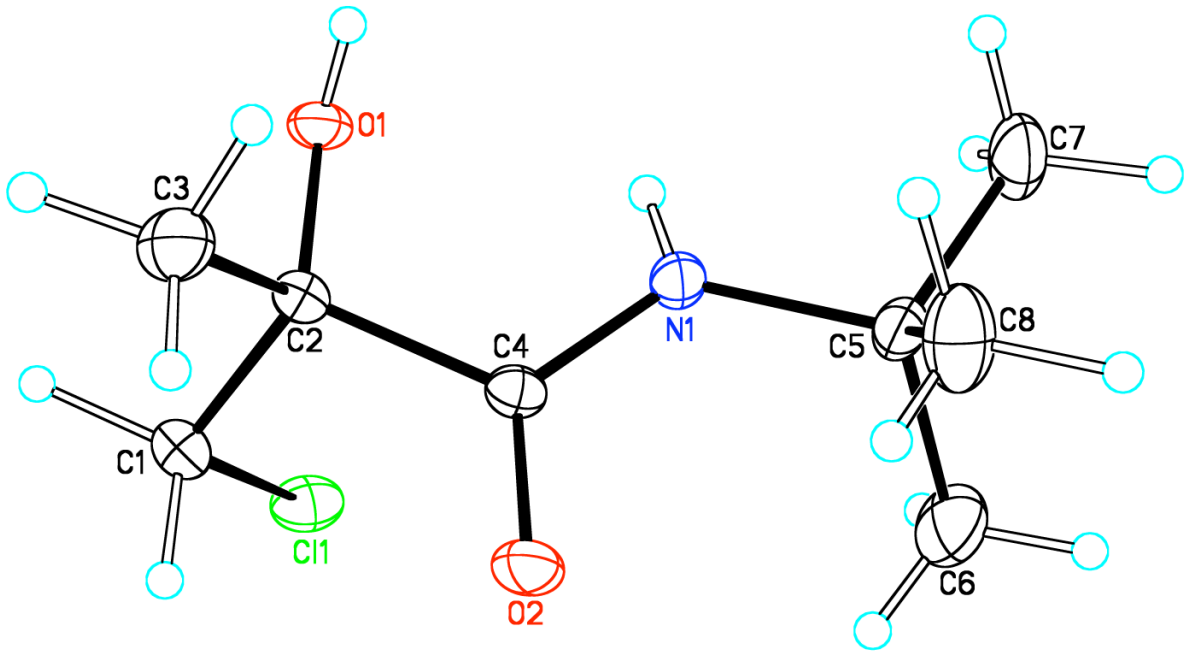
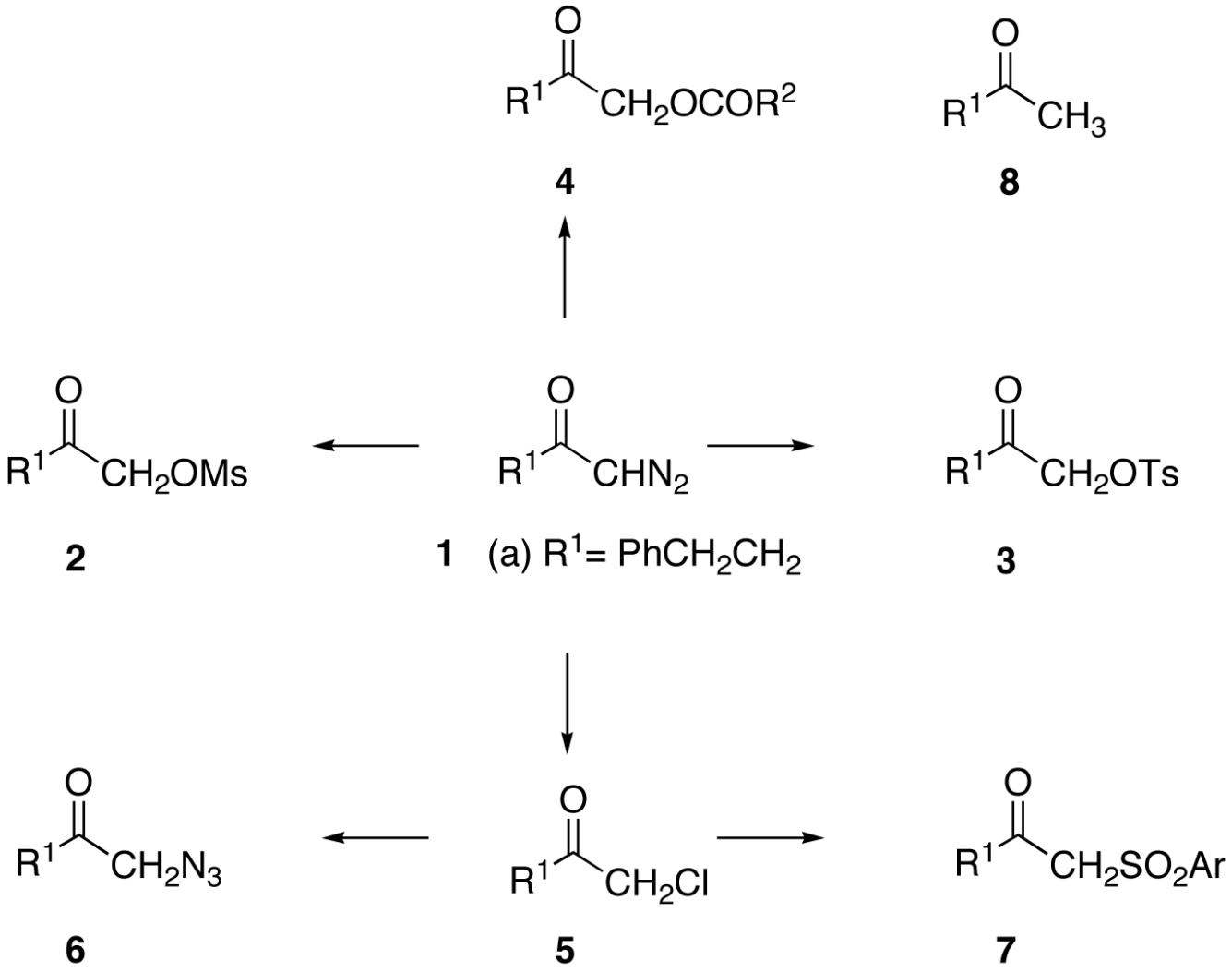
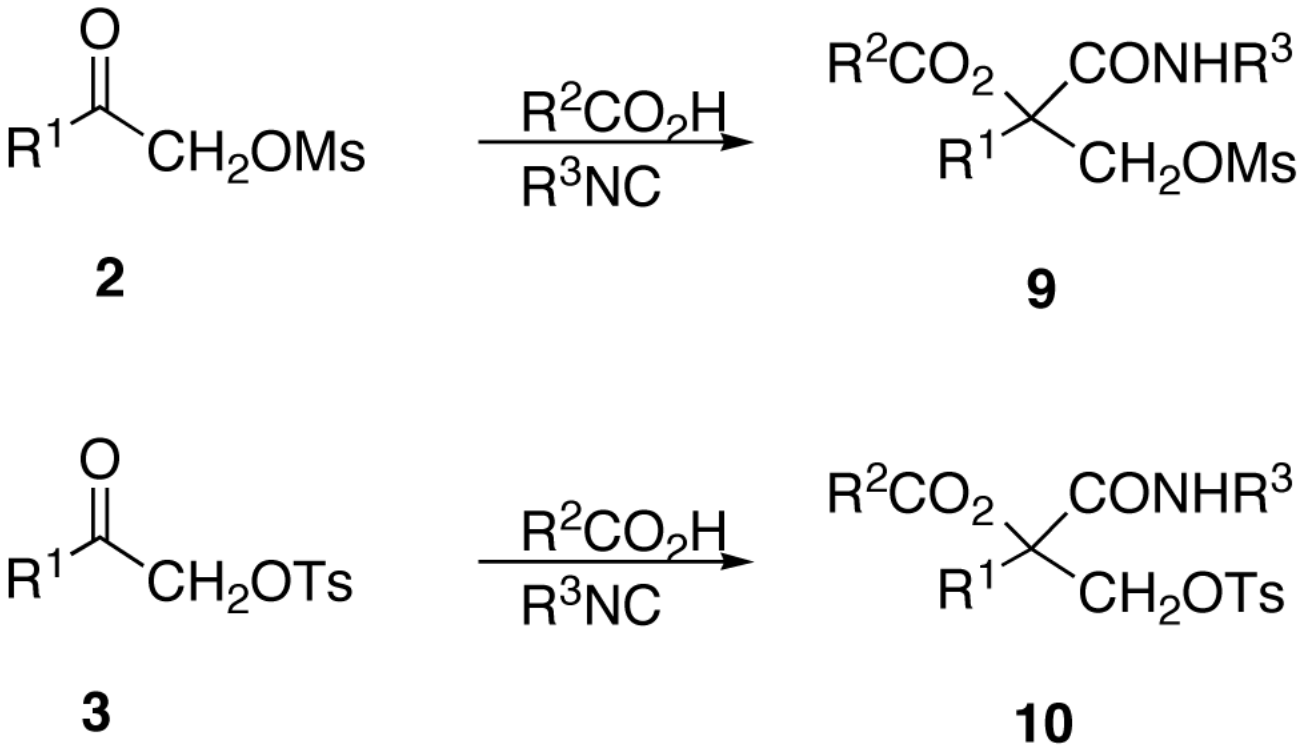


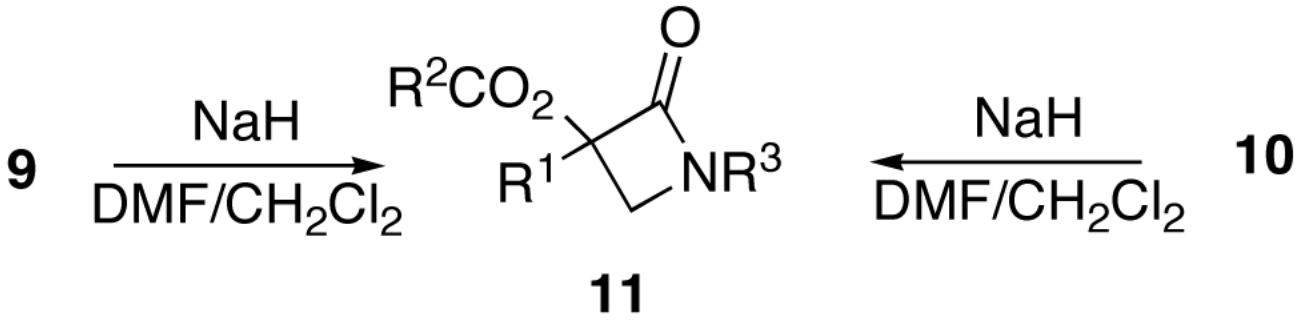
Figure 2.
ORTEP diagram of the x-ray crystal structure of **29**



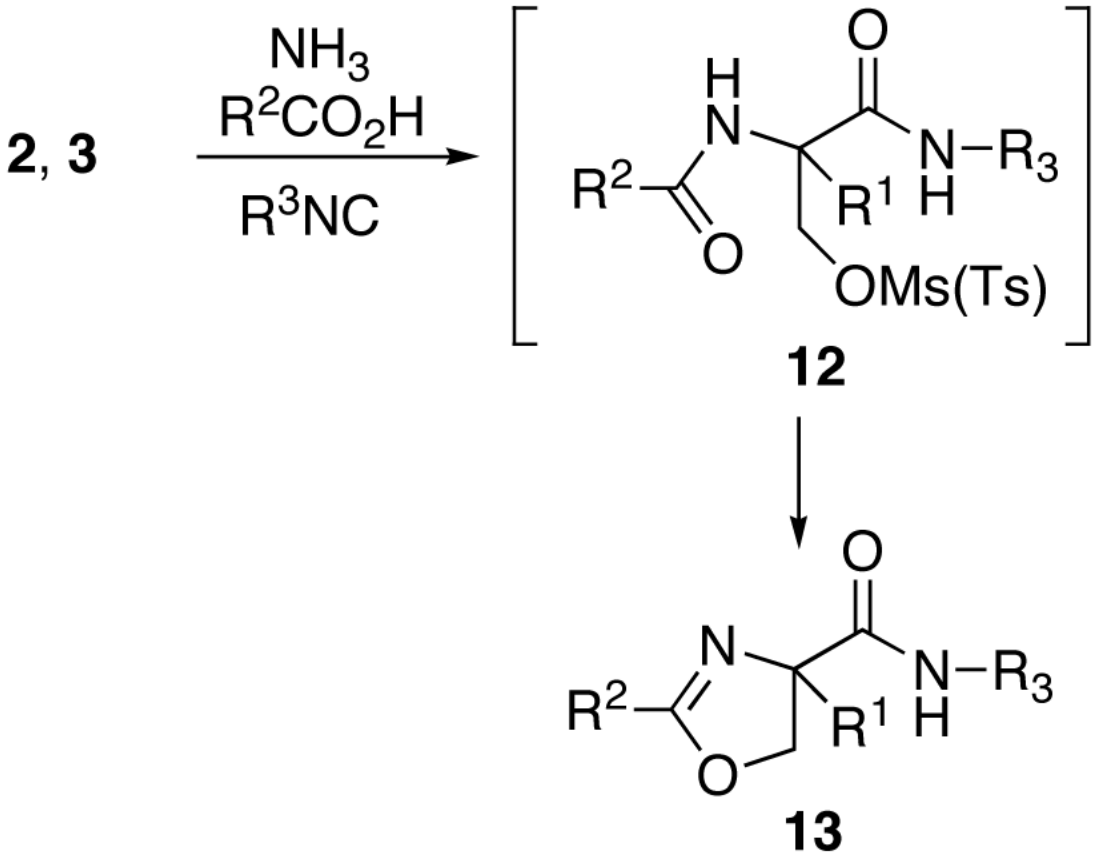
Scheme 1.



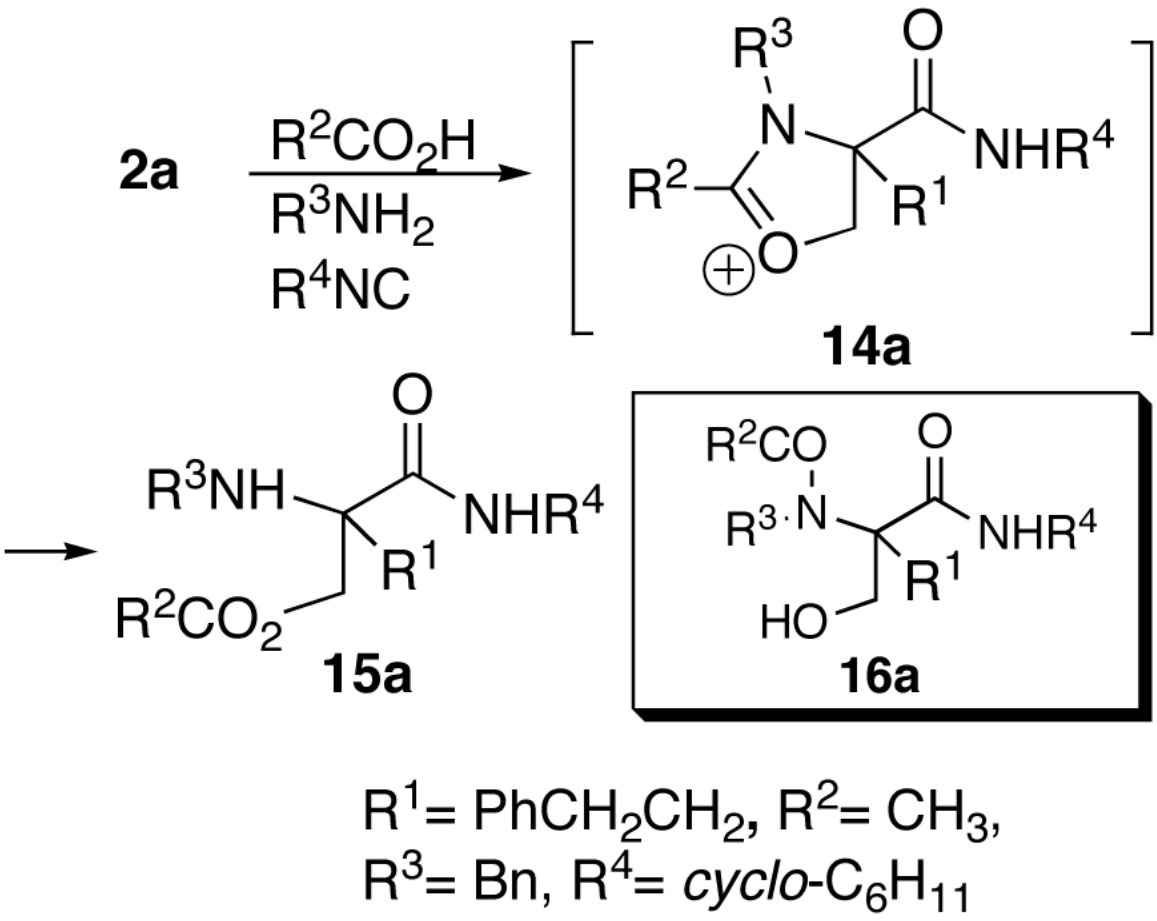
Scheme 2.



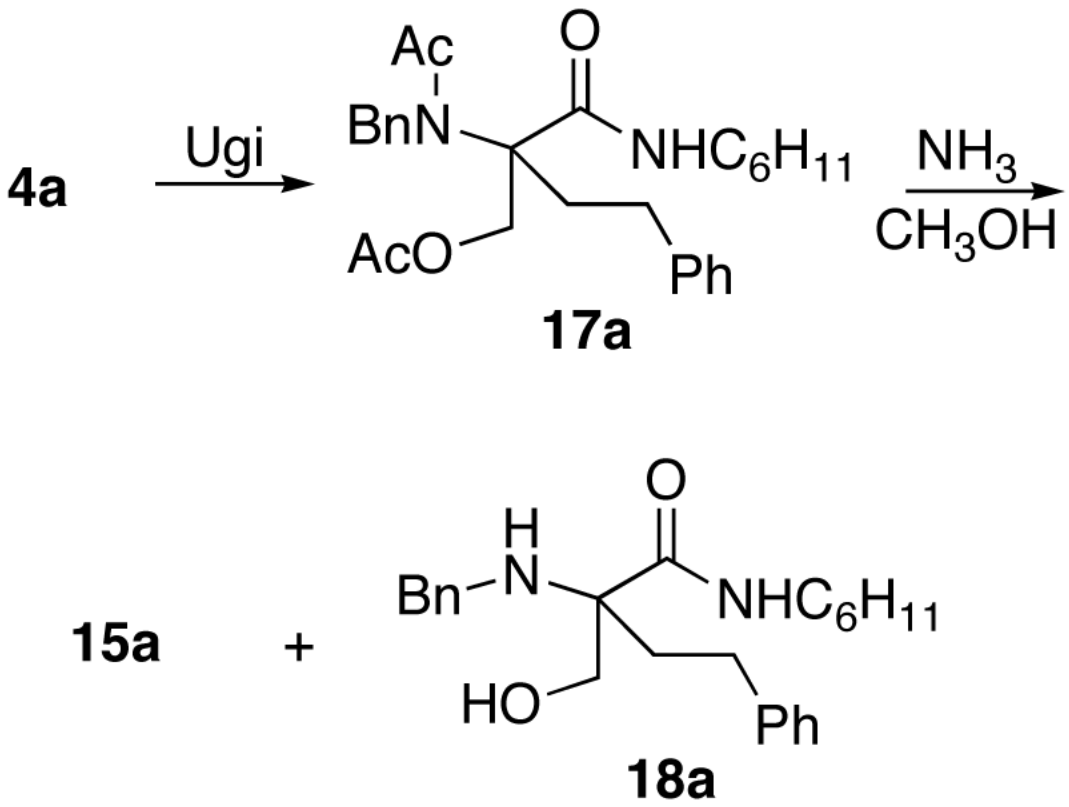
Scheme 3.



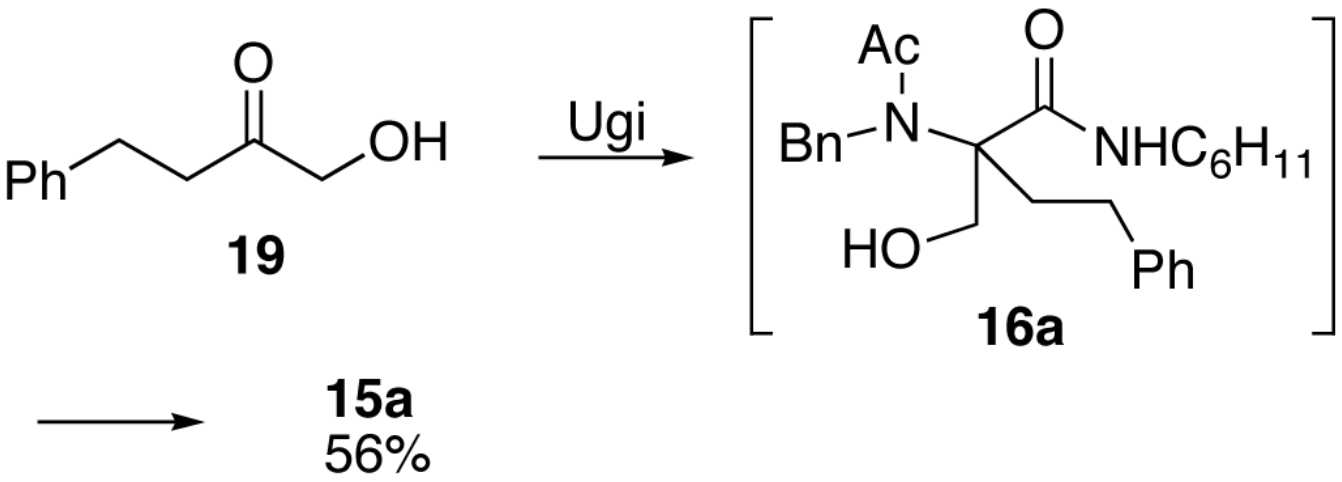
Scheme 4.



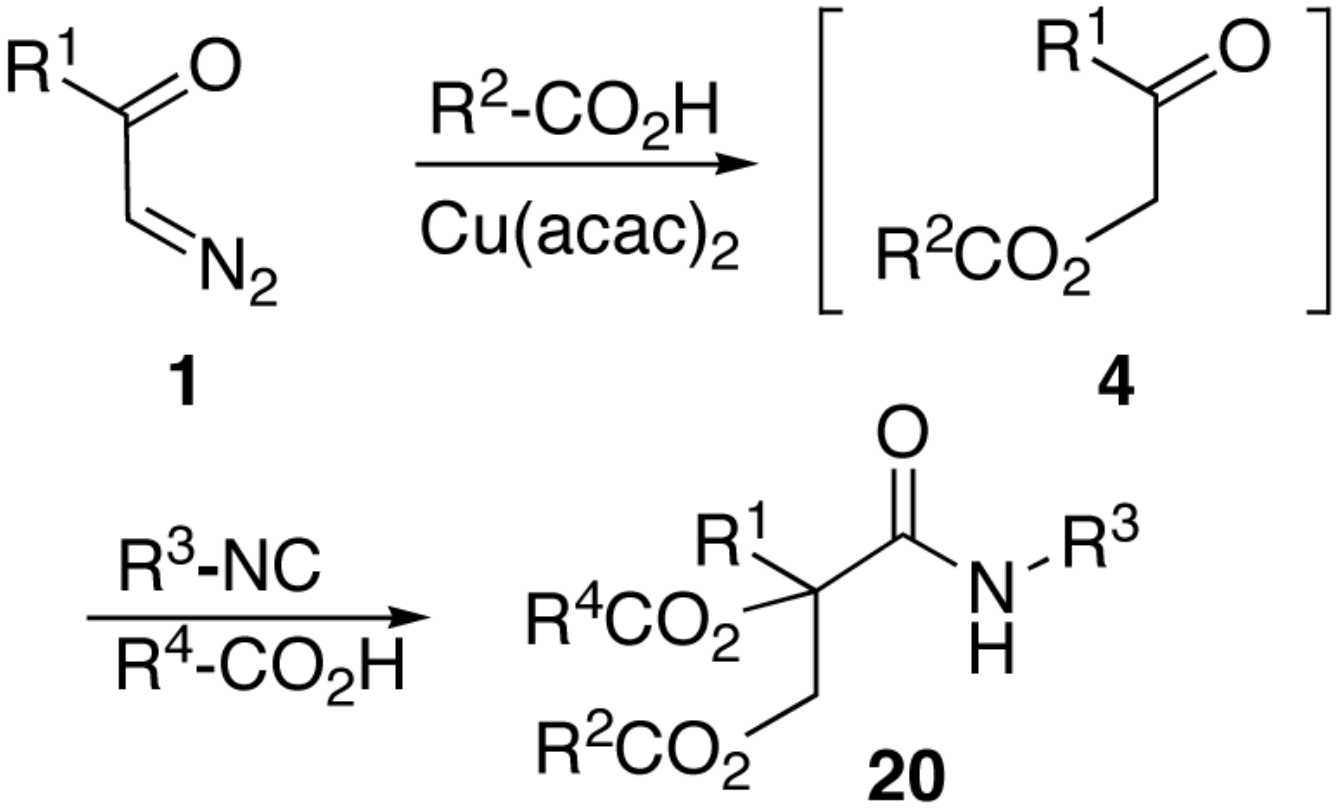
Scheme 5.



Scheme 6.



Scheme 7.



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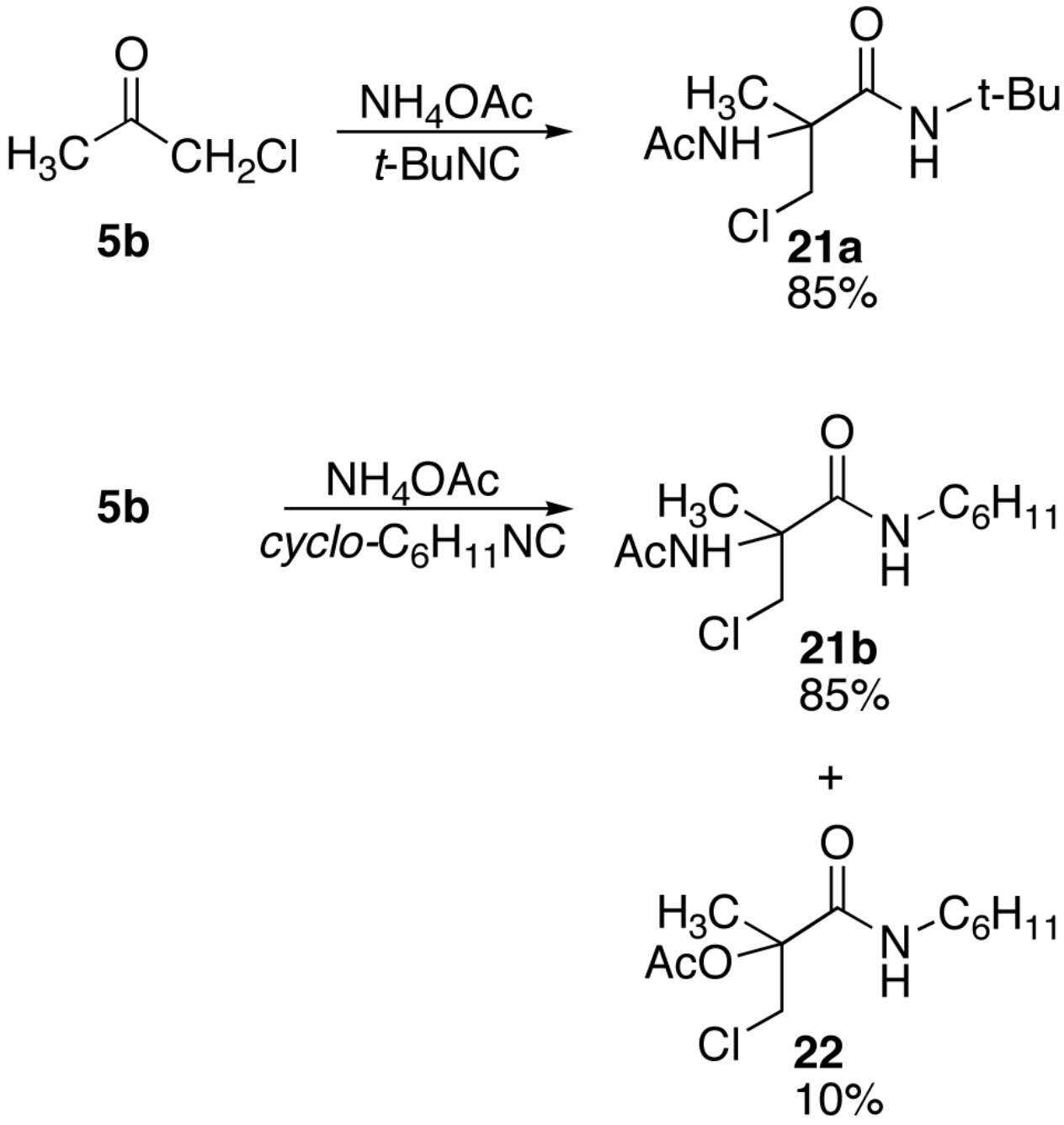

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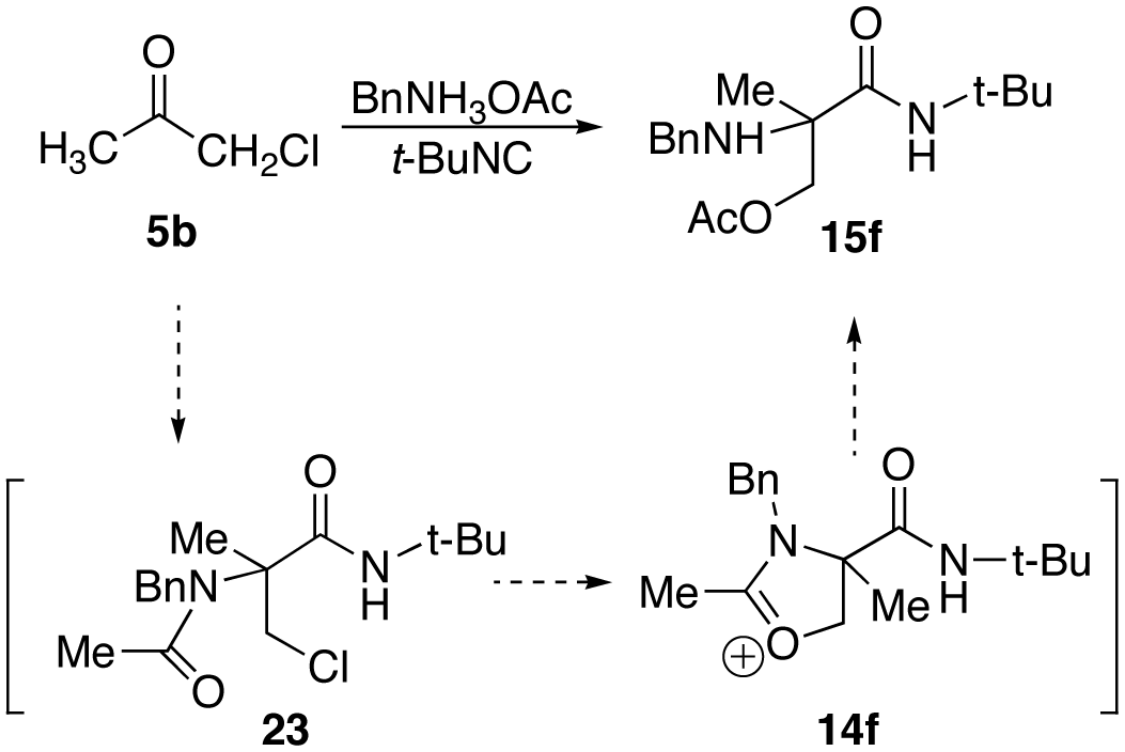
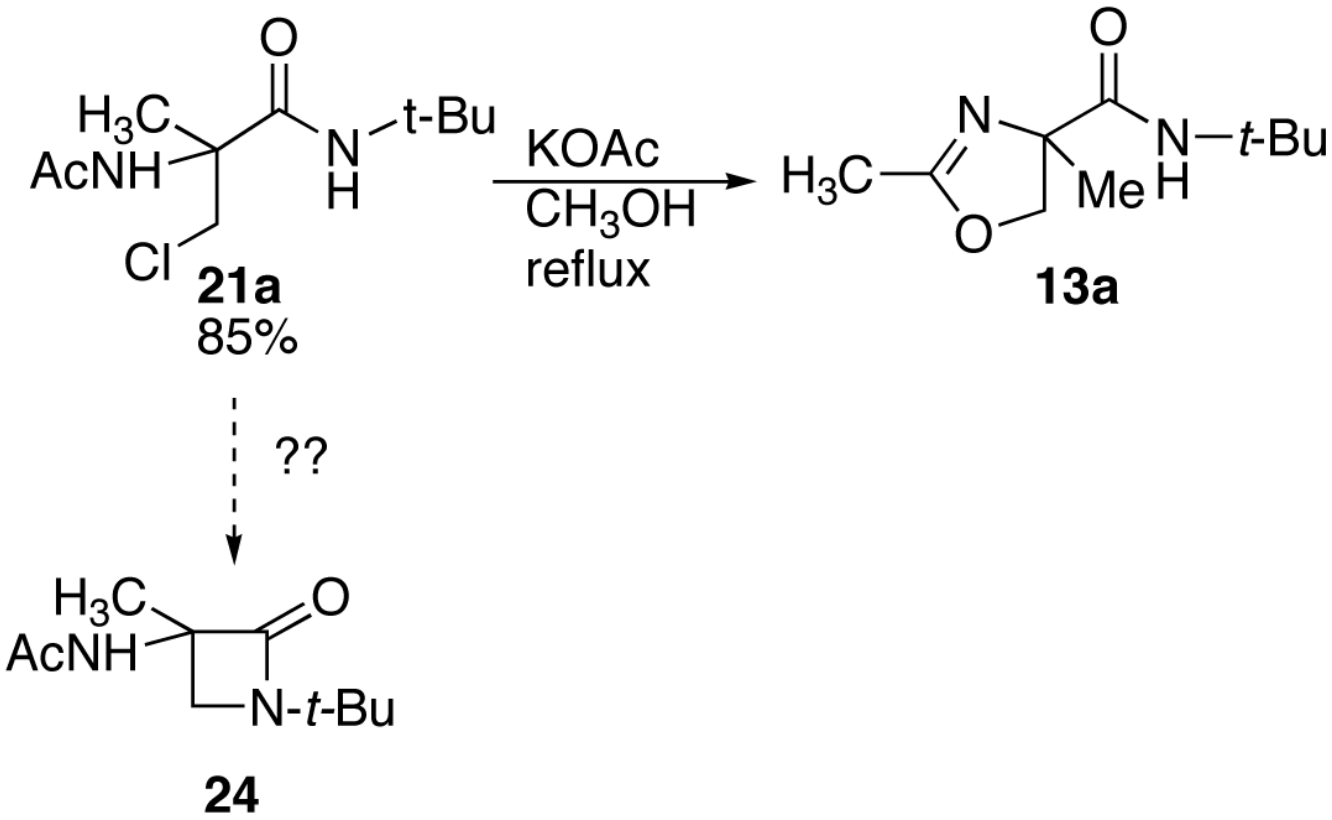
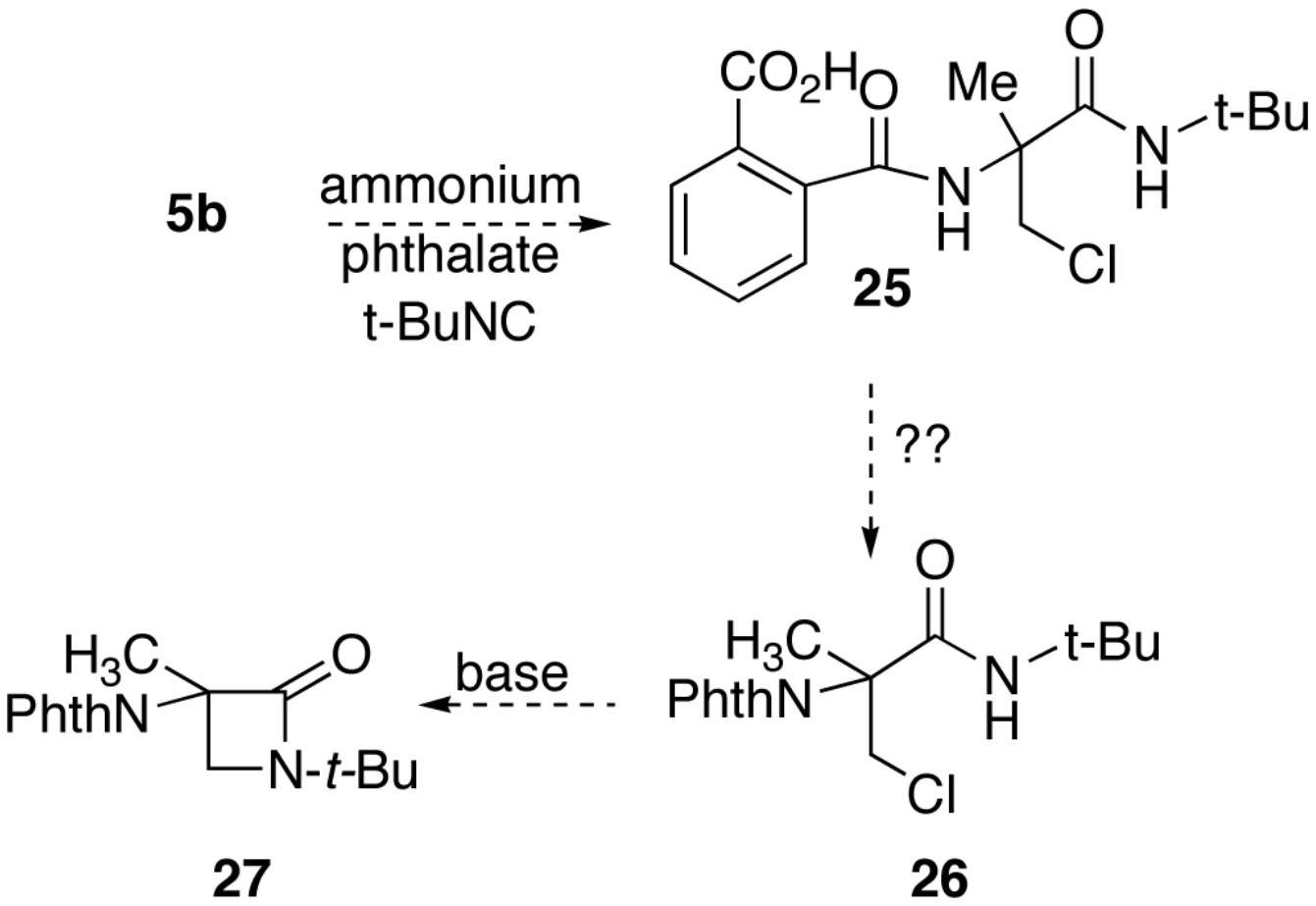


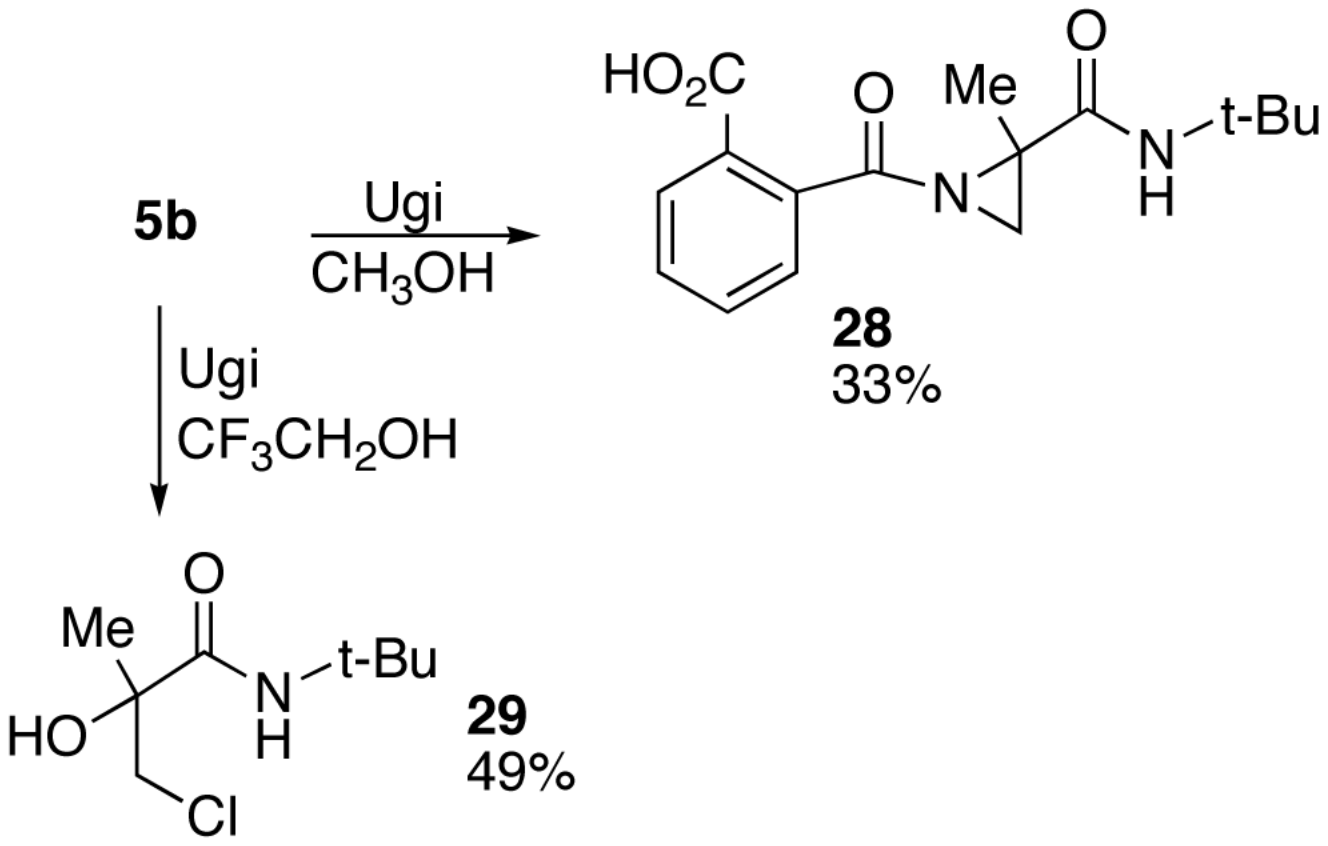
Scheme 10.



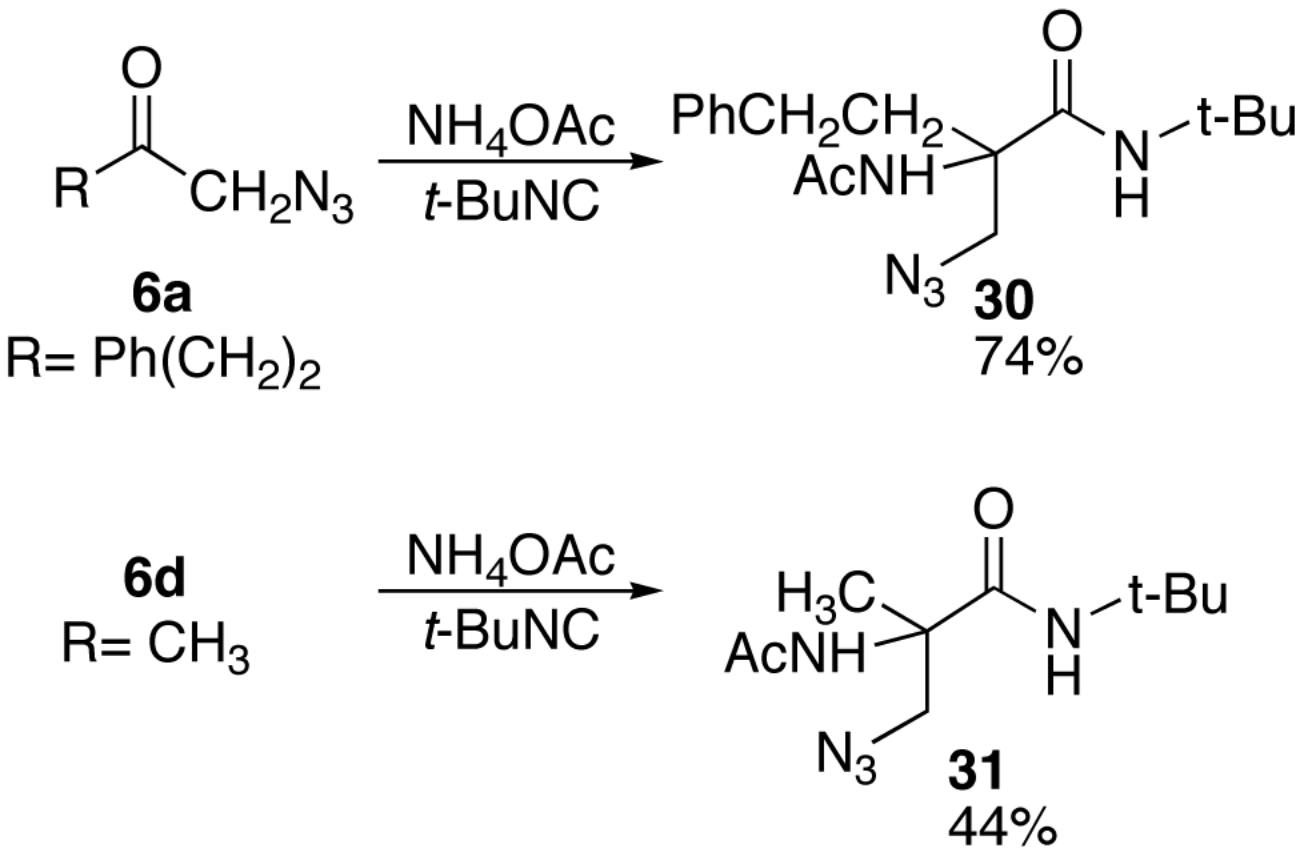
Scheme 11.



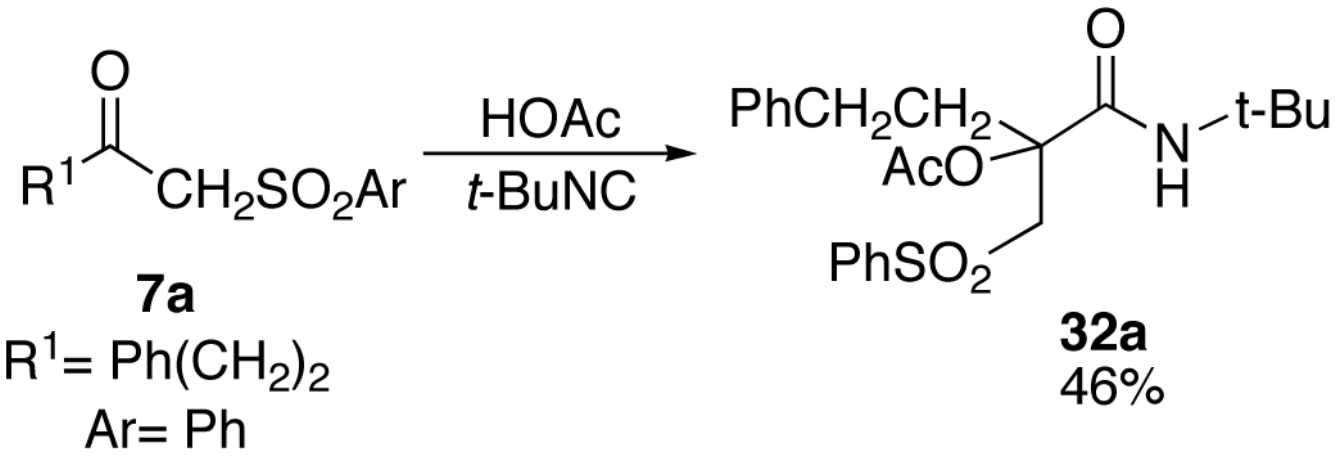
Scheme 12.



Scheme 13.



Scheme 14.



7a

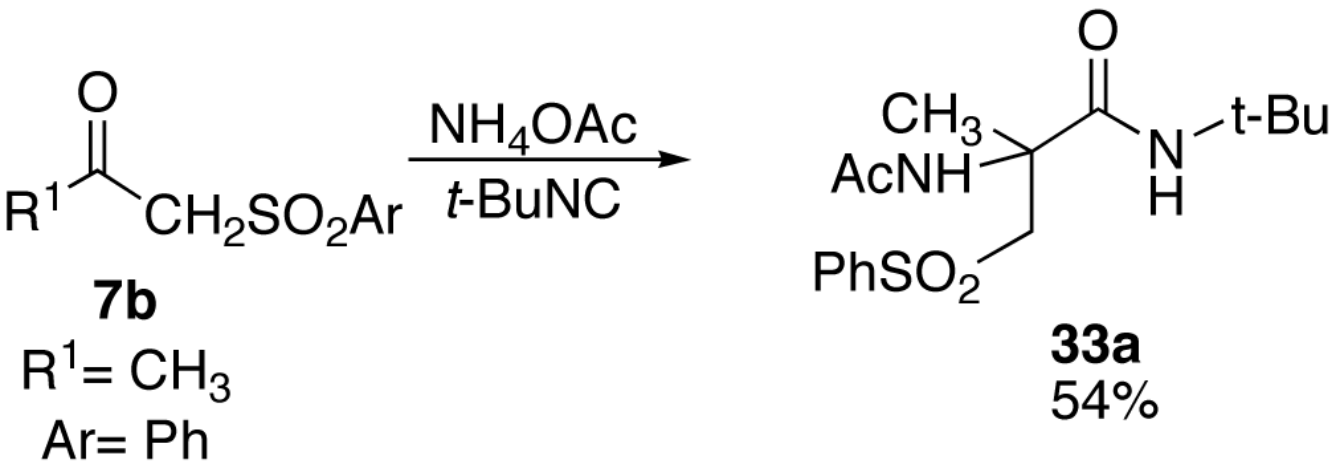
R^1= $Ph(CH_2)_2$

Ar= Ph

32a

46%

Scheme 15.



Scheme 16.

Table 1

Passerini Reactions of Mesyloxy- and Tosyloxyketones

Mesylate/Tosylate R^1 =	**R^2CO_2H R^2 =**	**R^3NC R^3 =**	**Product (yield)**
2a $Ph(CH_2)_2$	CH_3	*t*-Bu	**9a** (88%)
2a	Ph	*cyclo*-C_6H_{11}	**9b** (82%)
2a	CH_3	*cyclo*-C_6H_{11}	**9c** (80%)
2b *n*-C_7H_{15}	CH_3	*cyclo*-C_6H_{11}	**9d** (91%)
2c *cyclo*-C_6H_{11}	Ph	*n*-Bu	**9e** (80%)
2d Ph	CH_3	*cyclo*-C_6H_{11}	**9f** (18%)
3a $Ph(CH_2)_2$	Ph	*t*-Bu	**10a** (99%)
3a	Ph	*cyclo*-C_6H_{11}	**10b** (97%)
3b *n*-C_5H_{11}	CH_3	*cyclo*-C_6H_{11}	**10c** (97%)
3b	Ph	*cyclo*-C_6H_{11}	**10d** (99%)
3c *cyclo*-C_6H_{11}	CH_3	*t*-Bu	**10e** (80%)
3d Ph	Ph	*cyclo*-C_6H_{11}	**10f** (28%)

Table 2

Synthesis of Acyloxy-β-lactams 11 from Sulfonates 9 and 10

Sulfonate	Product (yield)
9c	**11a** (62%)
10a	**11b** (46%)
10b	**11c** (59%)
10c	**11d** (64%)
10d	**11e** (56%)

Table 3

Ugi Reactions of Mesyloxyketones 2 with Primary Amines

Mesylate 2; R^1 =	**R^2CO_2H R^2 =**	**R^3NH_2 R^3 =**	**R^4NC R^4 =**	**Product (yield)**
2a $Ph(CH_2)_2$	CH_3	Bn	*cyclo*-C_6H_{11}	**15a** (71%)
2a	*i*-Pr	allyl	*cyclo*-C_6H_{11}	**15b** (66%)
2b *n*-C_5H_{11}	Ph	Bn	*t*-Bu	**15c** (67%)
2b	*i*-Pr	allyl	*cyclo*-C_6H_{11}	**15d** (61%)
2b	CH_3	*i*-Pr	*cyclo*-C_6H_{11}	**9e** (70%)
2c *cyclo*-C_6H_{11}	*i*-Pr	*n*-Bu	*t*-Bu	**15e** (39%)
2d CH_3	CH_3	Bn	*t*-Bu	**15f** (74%)

Table 4

Four-Component Condensations of Diazoketones 1 Leading to Di-O-acylglyceramides 20

1 R^1 =	R^2CO_2H R^2 =	R^3NC R^4 =	R^4CO_2H R^4 =	**Product (yield)**
1a $Ph(CH_2)_2$	CH_3	*t*-Bu	CH_3	**20a** (94%)
1a	CH_3	*t*-Bu	$(CH_3)_2CH$	**20b** (90%)
1a	Ph	EtO_2CCH_2	C_7H_{15}	20c (72%)
1b *n*-C_5H_{11}	$(CH_3)_2CH$	*t*-Bu	$CbzNHCH_2$	**20d** (70%)
1b	Ph	*cyclo*-C_6H_{11}	CH_3	**20e** (80%)
1c *cyclo*-C_6H_{13}	C_7H_{15}	*n*-Bu	CH_3	**20f** (70%)
1c	$NCCH_2$	EtO_2CCH_2	Ph	**20g** (76%)
1d CH_3	$(CH_3)_2CH$	*n*-Bu	$CbzNHCH_2$	**20h** (71%)
1d	$H(CH_2OCH_2)_3$	*t*-Bu	C_7H_{15}	**20i** (58%)

Table 5

Passerini Reactions of α-Sulfonylketones 7

7	R^2CO_2H R^2 =	R^3NC R^3 =	Product (yield)
7a R^1= $Ph(CH_2)_2$ Ar= Ph	CH_3	*t*-Bu	**32a** (46%)
7b R^1= CH_3 Ar= Ph	CH_3	*n*-Bu	**32b** (40%)
7b	Ph	*t*-Bu	**32c** (50%)
7b	$(CH_3)_2CH$	*cyclo*-C_6H_{11}	**32d** (69%)
7c R^1=CH_3 Ar= *p*-FC_6H_4	Ph	*cyclo*-C_6H_{11}	**32e** (40%)
7c	Ph	*t*-Bu	**32f** (36%)

Table 6

Ugi Reactions of α-Sulfonylketones 7

7	R^2CO_2H R^2 =	R^3NH_2 R^3 =	R^4NC R^4 =	Product (yield)
7b $R^1 = CH_3$ Ar= Ph	CH_3	H	*t*-Bu	**33a** (54%)
7b	Ph	H	*t*-Bu	**33b** (<5%)
7b	CH_3	H	CH_2CO_2Et	**33c** (64%)
7c $R^1 = CH_3$ Ar= *p*-FC_6H_4	CH_3	H	*n*-Bu	**33d** (51%)