ORGANIC LETTERS

1999
Vol. 1, No. 6
883−886

New Synthetic Technology for the Synthesis of Hindered α-Diazoketones via Acyl Mesylates

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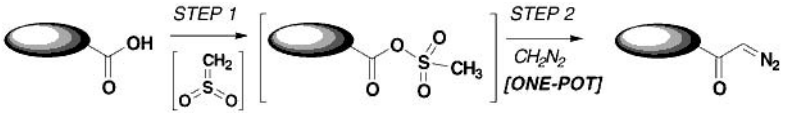
Received July 7, 1999

ABSTRACT



A mild and reliable one-pot protocol for the elaboration of sterically demanding carboxylic acids into α-diazoketones via acyl mesylates has been developed. Aside from delineating the reaction parameters which render this strategy quite general for hindered carboxylic acids, we have directly proven the existence of the fleeting acyl mesylate group as the reactive species in these reactions and shed light onto the differing mechanisms which are operative in the activation of hindered and simple carboxylic acids with methanesulfonyl chloride.

α-Diazoketones are versatile synthetic intermediates with a plethora of uses including dipolar cycloadditions, alkene, C−H, and X−H insertions, ylide formation, homologation of carbonyl compounds, and the classic Arndt−Eistert synthesis.[1] Although there are numerous methods for the preparation of these useful synthons,[2] we encountered several instances during our total synthesis of the CP molecules[3] wherein the synthesis of extremely hindered α-diazoketones from the corresponding carboxylic acids was inefficient or even impossible using previously described synthetic methods. Herein, we present a new method which is specifically suited for the one-pot preparation of sterically encumbered α-diazoketones in high yield.

The current method takes advantage of the highly reactive nature of the acyl mesylate species in order to activate sterically hindered acids for attack by diazomethane. Although a few scattered reports on the use of acyl mesylates are present in the literature, there is no definitive evidence that the intermediates of these reactions are actually acyl mesylates.[4c] Aside from demonstrating the generality of this new one-pot protocol, we have accumulated spectroscopic evidence which directly proves the existence of acyl mesylates for the first time. We have also reinvestigated some previous reports[4] which claimed to employ acyl mesylates and have determined that, in most cases, symmetrical anhydrides are the actual intermediates present as a result of sulfonyl chloride-mediated dehydration.

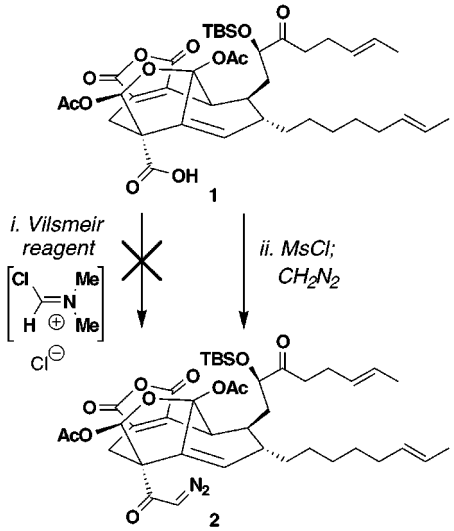
The need for a mild and reliable procedure for the preparation of α-diazoketones arose from our studies on the total synthesis of the CP molecules[3] in which the venerable

(1) Askani, R.; Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 126.
(2) Reference 1, p 126. See also: Atkinson, R. S. In *Comprehensive Organic Synthesis*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, p 246.
(3) Part 1: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 1669. Part 2: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem. Int. Ed.* **1999**, *38*, 1676. For an additional rationale for the employment of acyl mesylates to construct hindered diazoketones, see Scheme 9 of Part 1.
(4) (a) Dunn, A. D.; Mills, M. J.; Henry, W. *Org. Prep. Proced. Int.* **1982**, *14*, 396. (b) Chandrasekaran, S.; Turner, J. V. *Synth. Commun.* **1982**, *12*, 727. (c) Jászay, Z. M.; Petneházy, I.; Töke, L. *Synthesis* **1989**, 745. For work on acyl fluorosulphonates, see: Olah, G. A.; Narang, S. C.; Garcia-Luna, A. *Synthesis* **1981**, 790.

10.1021/ol990790l CCC: $18.00
Published on Web 08/31/1999

Arndt−Eistert homologation[5] was utilized to install the quartenary center present in the natural products. The resistance of the extremely hindered (concave situated) carboxylic acid group of **1** to conversion to the corresponding acid chloride with Vilsmeir reagent[6] even under forcing conditions (Scheme 1) sparked our efforts to develop an

Scheme 1[a]



[a] Reagents and conditions: i, Vilsmeir reagent (excess), THF: CH_3CN (2:1), −20 to 25 °C, 10 h, then 1 h sonication, ca. 30% decomposition, ca. 70% methyl ester after addition of CH_2N_2; ii, MsCl (5.0 equiv), Et_3N (10 equiv), THF, −50 to −10 °C, 5 min, then CH_2N_2 (solution in anhydrous Et_2O), 1 h, 86%.

operationally simplistic protocol for hindered carboxyl activation. We reasoned that a highly reactive reagent such as sulfene (produced from methanesulfonyl chloride and a suitable base) might rapidly engage even the most hindered carboxylic acids such as **1** to yield an activated species (acyl mesylate) which would rapidly react with diazomethane to produce the desired α-diazoketone. In the event, treatment of acid **1** with MsCl/Et_3N at −10 °C for 3 min followed by addition of CH_2N_2 at 0 °C afforded the α-diazoketone **2** in 86% yield.

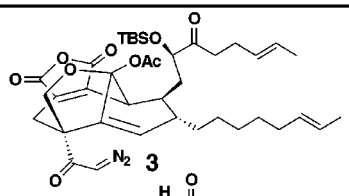
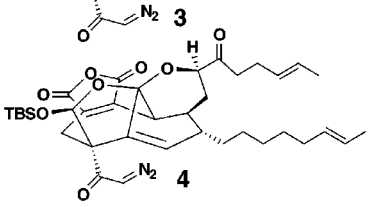
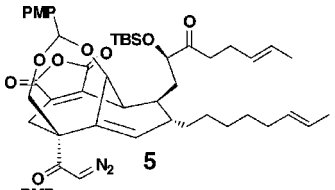
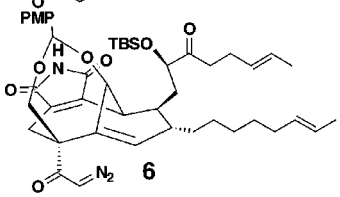
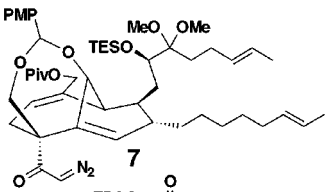
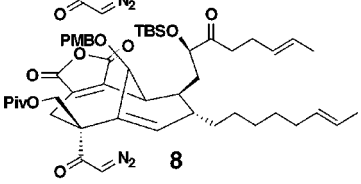
While traveling through the CP "synthetic labyrinth" [3] we had the opportunity to perform this reaction on several substrates in our search for a final synthetic route (Table 1). Acid labile functionalities (as seen in examples **4**−**7**), base-sensitive functionalities (as seen in examples **3**−**5** and **8**), and the presence of the maleimide functionality (**6**) are compatible with the developed conditions.

In most cases, the crude diazoketones were suitable for Wolff rearrangement after aqueous workup, thus completing the Arndt−Eistert homologation. Indeed, the reliability of

(5) Arndt, F.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1935**, *68B*, 200. We had identified the Arndt−Eistert reaction as the most prudent method to complete the quartenary center after a series of model studies which will be delineated in a full account of ref 3.

(6) For leading references, see: Marson, C. M.; Giles, P. R. *Synthesis Using Vilsmeir Reagents*; CRC Press: Boca Raton, FL, 1994.

Table 1. CP Diazoketone Intermediates Synthesized

Diazoketone[a]	Yield (%)[b]
 **3**	73
 **4**	75
 **5**	88
 **6**	93
 **7**	95
 **8**	82

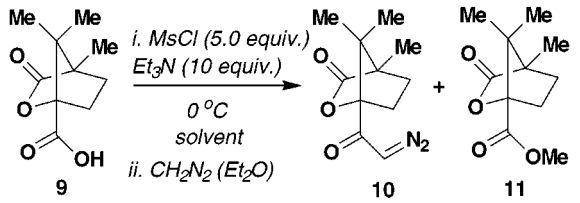
[a] Reactions were performed at 0.02−0.2 M in THF. Reactions were complete after ca. 30 min. Substrate **8** required 4 h for complete reaction. The synthesis of compounds **4** and **5** is reported in ref 3. Other compounds will be reported in the full account of ref 3. Temperatures as low as −50 °C worked; however, the reaction was usually carried out at −10 °C. [b] Isolated yield of pure diazoketone. Small amounts (1−8%) of methyl ester could be separated by flash chromatography (SiO_2, hexane:EtOAc 5:1 to 2:1).

this method, coupled with its extremely mild nature, was a pivotal element of our eventual completion of the CP molecules.[3]

Curiously, we found that in virtually all cases the reactions of hindered carboxylic acids furnished a small amount (1−8%) of the corresponding methyl ester regardless of the number of equivalents of MsCl/Et_3N (5 and 20 equiv lead to the same result) or the time allotted for acyl mesylate generation (3 and 15 min lead to the same result). We reasoned that the methyl ester byproduct must arise from small amounts of symmetrical anhydride which are produced in the first step of the reaction. Verification of this hypothesis evolved from experiments on more simple acids (vide infra).

As we turned our attention to other sterically hindered carboxylic acids in order to establish the generality of the protocol, we discovered a pronounced solvent effect on the reaction. Scheme 2 illustrates the effect of different solvents

Scheme 2. Solvent Effects on the Formation of Diazoketone **10**[a]



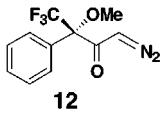
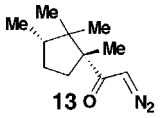
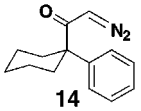
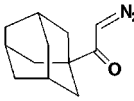
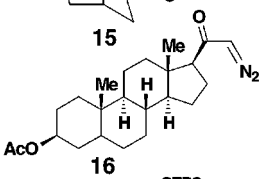
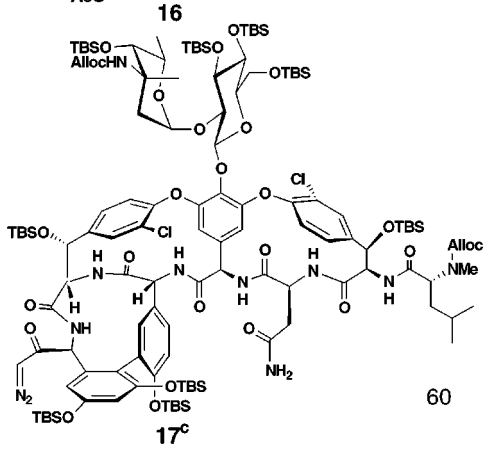
Entry[a]	Solvent	Ratio (10:11)[b]	Yield (%)[c]
1	pyridine	1:3	90
2	toluene	1:1	83
3	THF	2:1	81
4	acetonitrile	6:1	86

[a] All reactions were performed on a 1.0 mmol scale at 0.2 M in the indicated solvent. Entry 1 was performed without added Et_3N. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Total isolated yield of **10** + **11**.

on the ratio of desired α-diazoketone **10** to the methyl ester byproduct **11** in the reaction of (1*S*)-(−)-camphanic acid **9**. Not surprisingly, in the cases in which triethylamine is used as the base (entries 2−4), a general trend is observed in which more polar solvents favor formation of the diazoketone, presumably due to a stabilizing effect on the polar acyl mesylate intermediate (vide infra). Table 2 further demonstrates the generality of this condition utilizing acetonitrile as solvent with a variety of hindered acids. Particularly striking is the selective conversion of the vancomycin derivative **17**[7] to the corresponding diazoketone, containing no less than nine amides and a multitude of sensitive and easily epimerizable centers. This task was also accomplished without dehydration of the more easily accessible primary amide to the corresponding nitrile.[8] We have also found that $TMSCHN_2$ may be used as an alternative to CH_2N_2 to attack acyl mesylates; however, reaction times are considerably longer (ca. 8 h at 0 °C).[9]

Although the formation of the acid chloride of carboxylic acids is the most logical route to α-diazoketones from simple, sterically unblocked acids, we sought to understand the mechanism of the reaction by using these acids as it might explain the unpredictable appearance of the methyl ester

Table 2. Selected Hindered Diazoketones (**12**−**17**) Synthesized via the Corresponding Acyl Mesylates

Diazoketone[a]	Yield[b]
 **12**	86
 **13**	72
 **14**	88
 **15**	85
 **16**	71
 **17**[c]	60

[a] Reactions were performed at 0.2 M in acetonitrile at 0 °C except for acid **17**. Diazoketone generation was complete in *ca.* 1 h. Substrates **12**−**16** were commercially available. [b] Isolated yields of pure diazoketones.[c] See refs 7 and 8. 1,2-Dichloroethane was employed as solvent at −26 °C.

byproduct frequently observed in these reactions. We were indeed surprised to observe exclusive formation of the methyl ester accompanied by the corresponding symmetrical anhydride upon application of our protocol to several simple substrates. Performing the reaction under the conditions prescribed by Dunn et al.[4a] for the preparation of the acyl mesylate of cinnamic acid (**19**) (Scheme 3) led only to the corresponding symmetrical anhydride **20** along with some unreacted starting material (observed by ^1H NMR and IR spectroscopy of the crude reaction mixture).[10]

(7) For a related synthesis of compound **17**, see: Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 240; Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T., Koumbis, A, Natarajan, S. *Chem. Eur. J.* **1999**, in press. Special thanks to N. Winssinger for a generous sample of **17**.

(8) In this instance, 1,2-dichloroethane proved to be a superior solvent to acetonitrile. The dehydration of primary amides to the corresponding nitriles with methanesulphonyl chloride is known: see ref 4a. Acid **17** is completely unreactive with conventional esterification methods due to the extreme steric shielding present in its vicinity.

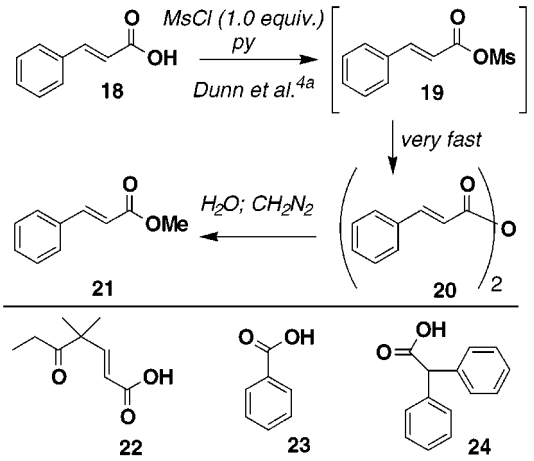
(9) The acid chlorides which we have tried are unreactive to $TMSCHN_2$.

(10) The use of methanesulfonyl chloride in the synthesis of symmetrical anhydrides is known: Nangia, A.; Chandrasekaran, S. *J. Chem. Res., Synop.* **1984**, 100.

(11) For the synthesis of **25**, see: Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H.-X. *J. Am. Chem. Soc.* **1999**, *121*, 4724. J. Pfefferkorn is gratefully acknowledged for providing a generous sample of **25**.

(12) Brewster, J. H.; Ciotti, C. J., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6214.

Scheme 3. Reinvestigation of the Chemistry of Acyl Mesylates

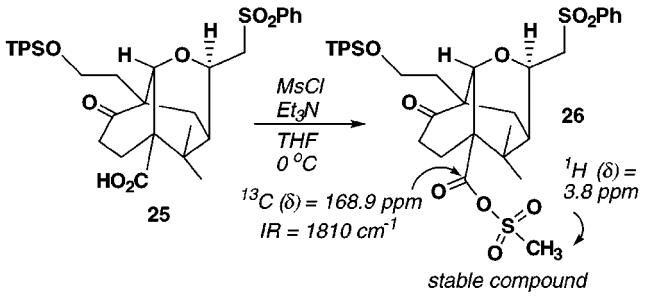


In the case of acids **18** and **22**−**24**, the corresponding symmetrical anhydride reacted slowly or not at all with diazomethane. Aqueous workup of the reaction hydrolyzed the anhydride, thus liberating the corresponding carboxylic acid which was quickly trapped with diazomethane to furnish the methyl ester. It should also be mentioned that despite repeated attempts using a variety of different conditions, we were unable to synthesize the acyl mesylates of compounds **18** and **22**−**24**.

To directly prove the existence of the acyl mesylate species, we employed the extremely hindered acid **25**.[11] Thus, treatment of **25** with Et_3N/MsCl at 0 °C for 10 min followed by filtration through Celite, evaporation, and dissolution in $CDCl_3$ allowed the first spectrocopic measurements to be taken of an acyl mesylate (**26**) (Scheme 4). Treatment with CH_2N_2 at 0 °C for 20 h led to the corresponding diazoketone in 30% yield (unoptimized).

(13) All compounds reported were fully characterized spectroscopically. In addition, all diazoketones exhibited a medium to strong intensity band in the infrared at 2105−2120 cm^{-1}. **General Procedure:** To a solution of (1*S*)-(−)-camphanic acid **9** in CH_3CN (0.2 M) was added Et_3N (10 equiv) at 0 °C. Freshly distilled methanesulphonyl chloride (5.0 equiv) was then added dropwise over 1 min. After 10 min an excess of CH_2N_2 (anhydrous ether solution) was added so that the color of the solution remained a constant light yellow. After 30 min, the reaction was complete as ascertained by TLC. The reaction was quenched upon addition of H_2O, and the product was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Concentration followed by flash chromatography (SiO_2, hexanes:EtOAc 5:1) furnished an inseparable mixture of diazoketone **10** and methyl ester **11** (6:1) in 86% yield.

Scheme 4. Synthesis and Characterization of the Stable Acyl Mesylate **26**



Previous investigators speculated that they were producing stable acyl mesylates (rather than simple anhydrides) because the nucleophiles which were employed (R-OH,[4b] R-NH_2,[4a,c] R-$NHNH_2$[4c]) may react with the symmetrical anhydrides before reacting with any remaining reagent (the remaining reagent then recycles the newly formed acid). In 1955, Brewster and Ciotti reported a similar phenomenon of complementary reactivity using tosyl chloride.[12] Thus, the dehydrative properties of sulfonyl chlorides can be easily mistaken for the intermediacy of an acyl sulfonate. In the case of hindered carboxylic acids (Tables 1 and 2), the formation of symmetrical anhydrides is disfavored *vis-à-vis* the formation of an acyl mesylate species for steric reasons. This fortuitous reactivity difference allows rapid formation of α-diazoketones via these highly reactive intermediates.[13]

In conclusion, we have developed a very mild one-pot synthesis of α-diazoketones from extremely hindered carboxylic acids, directly proven the intermediacy of acyl mesylates in these reactions, and shed light on the substrate-dependent mechanisms which are operative in the synthesis of acyl mesylates.

Acknowledgment. We thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, a postdoctoral fellowship from the Korea Science and Engineering Foundation (H.-S.C.), doctoral fellowships from the National Science Foundation (P.S.B.) and Boehringer Ingelheim (Y.H.), and grants from Pfizer, Glaxo, Merck, Schering Plough, Hoffmann-LaRoche, DuPont, and Abbott Laboratories.

OL990790L