Nucleophilic Catalysis with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) for the Esterification of Carboxylic Acids with Dimethyl Carbonate

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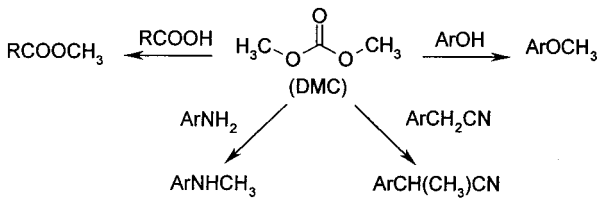
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is an effective nucleophilic catalyst for carboxylic acid esterification with dimethyl carbonate (DMC). The reaction pathway of this new class of nucleophilic catalysis has been studied. A plausible, multistep mechanism is proposed, which involves an initial *N*-acylation of DBU with DMC to form a carbamate intermediate. Subsequent *O*-alkylation of the carboxylate with this intermediate generates the corresponding methyl ester in excellent yield. In the absence of DBU or in the presence of other bases, such as ammonium hydroxide or *N*-methylmorpholine, the same reaction affords no desired product. This method is particularly valuable for the synthesis of methyl esters that contain acid-sensitive functionality.

Introduction

Methylation of alcohols, amines, carboxylic acids, and activated methylenes is an important process in chemistry. However, because of the environmental and human impact of using toxic and unsafe methylating reagents such as methyl iodide[1] or dimethyl sulfate,[2] the investigation of safer, generally applicable alternatives is imperative. As an alternative to these toxic methylating agents, dimethyl carbonate (DMC) has attracted considerable attention (Scheme 1) for the methylation of phenols,[3] anilines,[4] and activated methylenes.[5] DMC is nontoxic and generates CO_2 and methanol as byproducts during methylations. DMC is also a volatile liquid with a boiling point of 90 °C. Hence, the unreacted DMC can be easily recovered by distillation from the reaction mixture and reused. Furthermore, DMC has been shown to be quite selective in monomethylation of primary aromatic amines[4] and *C*-methylation of arylacetonitriles and arylacetoesters.[5] DMC is no longer synthesized from phosgene but from methanol and carbon dioxide catalyzed by transition metals.[6] However, the use of this "green reagent" (DMC) as a methylating regent requires temperatures above the boiling point of DMC. Therefore, autoclaves[4,5,7] or the use of asymmetrical carbonates[8] with a higher boiling point than DMC have to be employed. These restrictions lower the popularity of DMC as a widely used methylating reagent. The search for either a chemical or a physical means to accelerate the rate of methylation using DMC is a practical and challenging task.

Scheme 1



The methylation of phenols under autoclave conditions (120−200 °C) are believed to proceed through a $B_{AL}2$ mechanism[3f,9] in which the *O*-nucleophile attacks the methyl group of DMC.[3b] However, aromatic amines such as aniline are thought to proceed in a stepwise mechanism.[4a] Since arylacetonitriles and arylacetoesters yield only monomethylated compounds, they are also believed to go through several steps in which DMC acts as both a carboxymethylating agent and a methylating reagent.[5a−c] In the carboxymethylation step, it is postulated that the carbanion attacks the carbonyl of DMC ($B_{AC}2$ mecha-

(1) For examples using MeI with ROH, RNH_2, RCOOH, and RCH_2CN, see: (a) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169. (b) Ahmad, A. R.; Mehta, L. K.; Parrick, J. *Tetrahedron* **1995**, *47*, 12899. (c) Wang, T.; Lui, A. S.; Cloudsdale, I. S. *Org. Lett.* **1999**, *1*, 1835. (d) Abbotto, A.; Bradamante, S.; Facchetti, A.; Pagani, G. A. *J. Org. Chem.* **1997**, *62*, 5755.

(2) For examples using Me_2SO_4 with ROH, RNH_2, RCOOH, and RCH_2CN, see: (a) Merz, A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 846. (b) Voskresensky, S.; Makosza, M. *Synth. Commun.* **2000**, *30*, 3523. (c) Chakraborti, A. K.; Basak, A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014. (d) Ngooi, T. K.; So, R.; McGolrick, J. D.; Oudenes, J. Can. Pat. Appl. 2049274, 1993.

(3) (a) Lissel, M.; Schmidt, S.; Neumann, B. *Synthesis* **1986**, 382. (b) Shimizu, I.; Lee, Y. *Synlett* **1998**, 1063. (c) Bomben, A.; Selva, M.; Tundo, P.; Valli, L. *Ind. Eng. Chem. Res.* **1999**, *38*, 2075. (d) Tundo, P.; Trotta, F.; Moraglio, G.; Ligorati, F. *Ind. Eng. Chem. Res.* **1988**, *27*, 1565. (e) Barcelo, G.; Grenouillat, D.; Senet, J.-P.; Sennyey, G. *Tetrahedron* **1991**, *46*, 1839. (f) Selva, M.; Trotta, F.; Tundo, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 519.

(4) (a) Selva, M.; Bomben, A.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1041. (b) Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2001**, *66*, 677.

(5) (a) Bomben, A.; Marques, C. A.; Selva, M.; Tundo, P. *Tetrahedron* **1995**, *51*, 11573. (b) Tundo, P. *Pure Appl. Chem.* **2000**, *72*, 1793. (c) Selva, M.; Marques, C.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1323. (d) Tundo, P.; Trotta, F.; Moraglio, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1070.

(6) (a) Delledonne, D.; Rivetti, F.; Romano, U. *J. Organomet. Chem.* **1995**, *488*, C15−C19. (b) Ikeda, Y.; Sakaihori, T.; Tomishige, K.; Fujimoto, K. *Catal. Lett.* **2000**, *66*, 59. (c) Tomishige, K.; Ikeda, Y.; Sakaihori, T.; Fujimoto, K. *J. Catat.* **2000**, *192*, 355. (d) Sato, Y.; Yamamoto, T.; Souma, Y. *Catal. Lett.* **2000**, *65*, 123.

(7) (a) Thompson, R. B. U.S. Patent 4,513,146, 1985. (b) Loosen, P. C.; Tundo, P.; Selva, M. U.S. Patent 5,278,333, 1994.

(8) Perosa, A.; Selva, M.; Tundo, P.; Zordan, F. *Synlett* **2000**, 272.

(9) For classification of mechanisms for ester hydrolysis and formation, see: March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; Chapter 10, pp 334−338.

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Table 1. Reaction of Benzoic Acid with DMC in the Presence of Different Amine Bases

entry	amine base	time [h]	$PhCO_2Me$ [% yield][a]
1	none	16	0
2	NMM[b]	16	0
3	tributylamine	48	1
4	NH_4OH	24	0
5	DBU	2.5	97
6	DABCO	2.5	14
7	DMAP	2.5	2.5
8	DABCO	7.5	99
9	DMAP	22	99

[a] HPLC yield. [b] *N*-Methylmorpholine.

nism). In the methylation step, the anion of the corresponding intermediate attacks the methyl group of another molecule of DMC ($B_{AL}2$ mechanism).

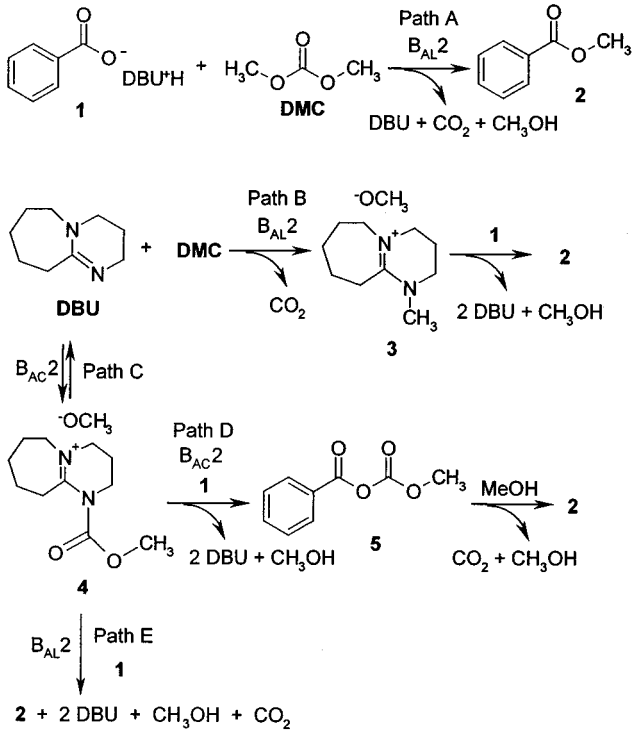
The exploration of DMC for the esterification of carboxylic acids is quite limited. To the best of our knowledge, this type of esterification has been described only in a few instances employing elevated temperature (175 °C) in autoclaves.[7] Furthermore, a review of the current literature illustrates a need for an in-depth study of the methylating power of DMC so that the proposed mechanisms can move from the realm of mere speculation to concrete confidence. As a result of the great potential for DMC as a environmentally friendly methylating reagent, a study was initiated to obtain a thorough understanding of the methylating process of DMC and to develop procedures for methylating without the use of autoclaves and elevated temperatures.

Results and Discussion

Reaction of Benzoic Acid with DMC in the Presence of Various Bases. Esterification of benzoic acid with DMC at 90 °C in the presence of a variety of amine bases (1 equiv) to form methyl benzoate (**2**) was first investigated (Table 1). In comparison with all other explored bases, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) dramatically shortened the reaction time. The conversion time to **2** using DBU is much shorter than the widely used acylation catalyst 4-(dimethylamino)-pyridine (DMAP). In 2.5 h, methyl benzoate formation is 97% complete using DBU but is only 2.5% complete using DMAP. Thus DBU leads to a shorter completion time. *N*-Methylmorpholine gave no product after 16 h. The use of tributylamine produced no methyl benzoate (**2**) after 3 h, and only 1% is produced after 48 h. With these experimental results, a fundamental question arises: Why is the reaction so fast with DBU? We began to speculate that the role of DBU is more than just as a proton scavenger and that perhaps it functions as a catalyst in the reaction.

Exclusion of $B_{AL}2$ Displacement by Kinetic Difference. Several reasonable mechanisms can be postulated (Scheme 2) for benzoate formation employing a combination of DMC and DBU. The first possible mechanism (path A) is a direct $B_{AL}2$ displacement, which is described for the reaction of phenols with DMC under different conditions.[3b] This mechanism is ruled out for two reasons. First, with a $B_{AL}2$ mechanism, the presence of 1 equiv of methanol should not dramatically reduce the conversion rate. However, when benzoic acid, DBU, and DMC are heated to reflux with 1 equiv of methanol, the reaction is much slower. We observed that without the added methanol, methyl benzoate (**2**) formation is complete (99%) within 3 h, but with extra methanol,

Scheme 2



methyl benzoate formation is still not complete after 24 h. The results could imply an unfavorable equilibrium caused by the addition of methanol (path C). However, it is also possible that the rate of the reaction is slowed by lowering the nucleophilicity of the carboxylate anion in the presence of additional methanol.[10] As previously mentioned, the reaction does not proceed when *N*-methylmorpholine is used as the base, and the use of DMAP requires a longer reaction time (22 h) for completion compared to DBU (3 h). This suggests that DMC is a poor electrophile under certain conditions. To initiate the esterification, DMC needs to be activated by a suitable catalyst to form a more reactive methylating species.

Dependence of Rate of Esterification on the Amount of DBU. If there is no direct $B_{AL}2$ displacement and the reaction rate is dependent on the amine base used, then the transition state most likely involves DBU itself (Scheme 2, path B or C). As mentioned before, esterification of benzoic acid with DMC can be completed within 3 h in the presence of 1 equiv of DBU. However, when only 0.2 equiv of DBU was used in a reaction of benzoic acid with DMC, the reaction rate dramatically decreased. After 17 h, only 2% of methyl benzoate (**2**) was formed. When 0.5 equiv of DBU was used, a total conversion of methyl benzoate was observed in 17 h as indicated by HPLC analysis. It is postulated that with 1 equiv of DBU, the initial diffusion-controlled deprotonation of carboxylic acid consumes all of the DBU, and only a slight amount of DBU is available via equilibrium to react with DMC to form an active intermediate. As more benzoic acid is converted to the ester, more DBU becomes available, and the rate of esterification accelerates. Consequently, the rate of reaction should be much slower in the initial stages, which is consistent with the kinetic

(10) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: New York, 1988; p 210.

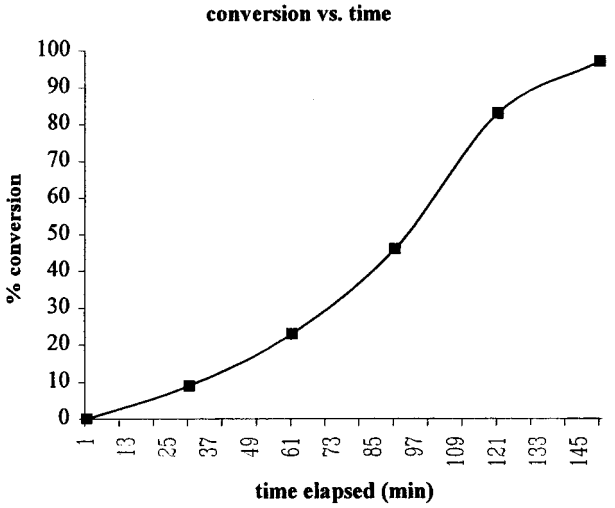
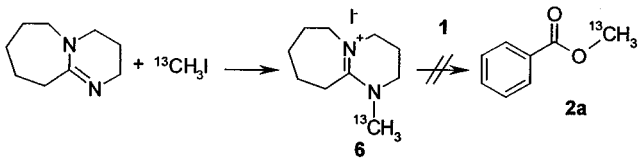


Figure 1. Rate of methyl benzoate formation with 1 equiv of DBU.

Scheme 3



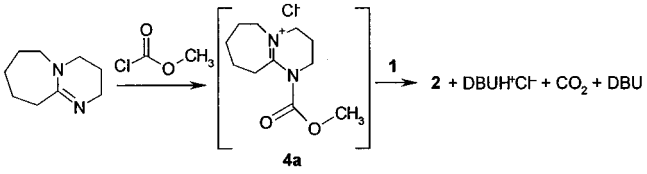
MS: *m/z* of cation = 168
^{13}C NMR $\delta_{N\text{-}CH3}$ = 42 ppm

data acquired in our experiment (Figure 1). The dependence of the reaction rate on the amount of DBU used strongly suggests that the esterification pathway involves a DBU-catalyzed step.

DBU-Containing Intermediate: DMC as a Methylating Agent. Since DMC can act as either a methylating or a carboxymethylating reagent toward DBU, two possible intermediates, **3** and **4**, are proposed (Scheme 2). The first intermediate (path B) involves the reaction of DBU with a methyl group of DMC to form an *N*-methylated-DBU salt (**3**), analogous to a known compound from the reaction of DBU and methyl iodide.[11] To discover if **3** is the active intermediate, labeled **3** was independently synthesized from $^{13}CH_3I$ and DBU (Scheme 3, **6**). A solution of benzoic acid, DBU, and salt-**6** in acetonitrile was heated to reflux overnight but failed to produce any labeled methyl benzoate (**2a**). ^{13}C NMR indicated a total recovery of salt-**6**. These outcomes clearly suggest that salt-**6** is not the active intermediate responsible for the formation of the methyl ester.

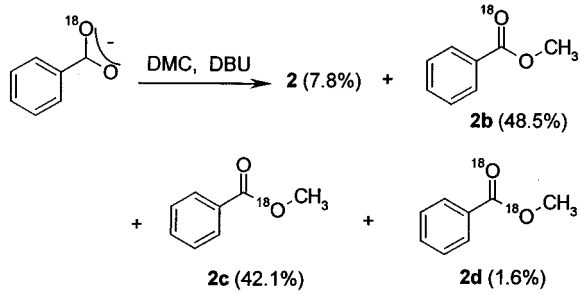
DBU-Containing Intermediate: DMC as a Carboxymethylating Agent. Attention now turned to DMC acting as a carboxymethylating reagent with DBU (Scheme 2, path C). It has been reported that reaction of carboxylic acids with alkyl chloroformate in the presence of a stoichiometric amount of triethylamine and a catalytic amount of DMAP affords the corresponding esters. This methodology is convenient; however, it utilizes a highly hazardous chloroformate that could generate a significant amount of symmetrical anhydride as the byproduct.[12] If DBU reacts with DMC to form carbamate (**4**), the presence of excess methanol should slow the formation of **4** since methanol can reverse the equilibrium. As previously stated, adding 1 equiv of methanol dramatically slows down the conversion rate. To support carbamate (**4**) as the likely intermediate during the esterification, an analogous carbamate (**4a**) was independently synthesized in situ from methyl chloroformate and an excess of DBU (Scheme 4). ^{1}H and ^{13}C NMR and MS spectra support the identity of the carbamate intermediate. When benzoate (**1**) was added to this mixture, a voluminous evolution of gas started within a few minutes and methyl benzoate (**2**) formed. As benzoate attacks the methyl group of carbamate (**4a**), CO_2 should evolve and DBU should be regenerated.

Scheme 4



MS: *m/z* of cation = 211
^{13}C NMR $\delta_{N(+)=C}$ = 171.5 ppm

Scheme 5



^{18}O-Labeling Study. Another question arises about carbamate (**4**) as the intermediate. Mixed anhydrides are known intermediates in the synthesis of methylcarbamates from amines and DMC.[13] Does the carboxylate react with **4** in a direct $B_{AL}2$ methylation (path E) or does it form an unsymmetrical anhydride, **5**, which is attacked by methanol to form ester **2** (path D)? The answer to this question was found in a labeling experiment. Labeled benzoic acid (with only one ^{18}O) was reacted with DBU and DMC (Scheme 5) at 90 °C. If the reaction proceeded through **5** (path D), then isotopomer **2** and **2b** will be the products in approximately a 1:1 ratio. The ratios of different isomers can be determined from GC−MS and IR analyses. However, the labeling study concluded that 90.6% of the methyl benzoate contains one oxygen-18 (isotopomers **2b** and **2c**). *This result supported the postulate that a direct O-alkylation of benzoate with carbamate (4) is the preferred mechanism for the formation of methyl benzoate (2)* (Figure 2). The small quantity of **2** and **2d** is most likely due to transesterification because prolonged heating of the reaction mixture could increase the amount of **2** and **2d**.

Synthetic Utility. To investigate the synthetic utility of this reaction, a variety of carboxylic acids were methylated using DMC as both a solvent and a reactant with 1 equiv of DBU (Table 2). All of the reactions were complete within 24 h. Since quantitative conversions were achieved in many cases, clean products can be isolated after simple aqueous acid and base washes

(11) Heidelberger, v. C.; Guggisberg, A.; Stephanou, E.; Hesse, M. *Helv. Chim. Acta.* **1981**, *64*, 399.

(12) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365.

(13) Aresta, M.; Quaranta, E.; *Tetrahedron* **1991**, *47*, 9489.

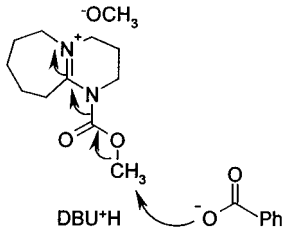
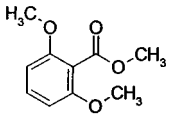
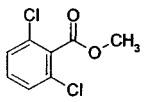
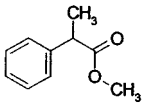
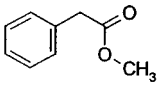
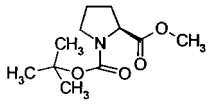
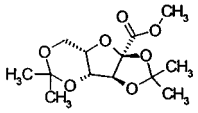


Figure 2. Proposed mechanism.

Table 2. DBU-Catalyzed Esterification with DMC: RCOOH → RCOOCH$_3$

Entry	Ester	Time [h]	Yield[a,b] [%]
1	 **7**	4	99
2	 **8**	24	99
3	 **9**	5	98
4	 **10**	6	98
5	 **11**	16	99
6	 **12**	16	99

[a] HPLC yield. [b] The identity of the methylated products was confirmed by ^{1}H and ^{13}C NMR and MS spectra.

without further purification. Not only can simple aromatic esters be synthesized, but also a sterically hindered ester (**7**, entry 1) and an unactivated ester (**8**, entry 2) can be as well. For a protected amino acid, *N*-α-*t*-Boc-L-proline (entry 5), the esterification yield was excellent. However, partial racemization (3.5%) for the isolated *N*-α-*t*-Boc-L-proline methyl ester (**11**) was detected by chiral HPLC. The ability to esterify *N*-α-*t*-Boc-L-proline and 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (entry 6) to form **11** and **12**, respectively, demonstrates another niche for this methodology. These esters, containing acid-sensitive functionalities, would not survive acid-catalyzed esterification conditions.[14]

Conclusions

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is generally used as a hindered base for enolate formation or as a proton scavenger. We discovered that DBU can function as an effective catalyst for carboxylic acid esterification with dimethyl carbonate (DMC) without autoclave conditions. The mechanism of this new class of nucleophilic catalysis[15] involves the reaction of DBU with DMC to form an unstable carbamate (**4**), which behaves as a highly activated methylating reagent. This carbamate then reacts with carboxylates to afford the respective methyl esters. Synthetic applications to a variety of carboxylic acids, including sterically hindered unactivated aromatic acids, an acid-sensitive amino acid, and a carbohydrate acid, were demonstrated with excellent yields. Investigation of DBU as a nucleophilic catalyst for other reactions is currently being conducted in our laboratory.

Experimental Section

All reagents were purchased from commercial suppliers and used without further purification. Methyl esters **2**,[16] **7**,[17] **8**,[18] **9**,[19] **10**,[16] **11**,[20] and **12**[21] are known compounds. The identity of the methylated products was confirmed by ^{1}H and ^{13}C NMR and MS spectra. Solvents used were of technical grade. ^{1}H and ^{13}C NMR spectra were recorded with Bruker FT-NMR spectrometer at 300 and 75 MHz, respectively. GC−MS analysis was performed on a ThermoFinnigan Trace MS with a Restek RTX-5 (15 mm × 0.25 mm) column. High-resolution mass spectroscopy (HRMS) was carried out on a ThermoFinnigan MAT-900 in electrospray mode. Other mass spectroscopy was performed on a Micromass LCT in electrospray mode. IR data were collected on a Nicolet Magna 550.

General Procedure for Esterification with DMC. DBU (1 equiv) was added to a 10% solution of carboxylic acid in DMC, and the resulting mixture was heated to reflux. Upon completion, the reaction mixture was cooled to room temperature and diluted with either CH_2Cl_2 or EtOAc and H_2O. The aqueous layer was removed, and the organic layer was washed with H_2O, twice with 2 M HCl or 10% aqueous citric acid, twice with saturated aqueous $NaHCO_3$, and twice with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the ester.

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(14) For an example of acid-catalyzed esterification, see: Nakao, R.; Oka, K.; Fukomoto, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 126.

(15) There is one other instance in which DBU was reported as a nucleophilic catalyst for the Baylis−Hillman-type reaction. See: Aggarwal, V. K.; Mereeu, A. *Chem. Commun.* **1999**, 2311.

(16) Commercially available from Aldrich.

(17) Tsuchida, E.; Hasegawa, E.; Komatsu, T. *Chem. Lett.* **1990**, 389−392.

(18) Walther, H.; Schlunegger, U. P.; Friedli, F. *Org. Mass. Spectrom.* **1983**, *18*, 572−575.

(19) De Luca, C.; Inesi, A.; Rampazzo, L. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1403−1407.

(20) (a) Harris, B. D.; Bhat, K. L.; Joullie, M. M. *Heterocyles* **1986**, *24*, 1045−1060. (b) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145−2151.

(21) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296−1309.