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LEWIS ACID - PROMOTED CYCLOPROPANATION OF α,β -UNSATURATED CARBONYL COMPOUNDS BY DIAZOCARBONYL COMPOUNDS. A FACILE SYNTHESIS OF 1,2-DISUBSTITUTED CYCLOPROPYLCARBONYL COMPOUNDS OF HIGH ISOMERIC PURITY

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Antimony pentafluoride promotes condensation of α , β -unsaturated aldehydes and ketones with diazocarbonyl compounds to form 1,2-disubstituted cyclopropylcarbonyl compounds in preparatively useful yields. Isomerization of the cyclopropylcarbonyl derivative by antimony pentafluoride produces the more stable geometrical isomer in high isomeric purity.

Diazo compounds react with a wide variety of unsaturated substrates to form cyclopropane derivatives under thermal and photochemical conditions or in the presence of transition metal catalysts.¹ However, only low yields of cyclopropanation products are usually reported for reactions of diazo compounds with α,β -unsaturated carbonyl compounds.^{2,3} The rapid formation of 1-pyrazolines, and their subsequent rearrangement to 2-pyrazolines, ³ limits effective cyclopropanation of these substrates. Although cyclopropane formation from diazo compounds without intervention of pyrazolines through ionic transformations has been described,⁴ only limited success has been realized with this strategy.^{4,5} Surprisingly, an alternate strategy of ionic addition by Lewis acid - activated unsaturated substrates to diazo compounds has not been explored. Lewis acid activation of carbonyl compounds is basic to the success of the well known aldehyde and ketone homologation reactions with diazo compounds⁶ and, as we now report, can be advantageously employed to effect ionic addition of α,β -unsaturated carbonyl compounds to diazo-carbonyl compounds with subsequent intramolecular nucleophilic displacement of nitrogen.

We have found that antimony pentafluoride effectively promotes rapid reactions of α , β -unsaturated aldehydes and ketones with diazocarbonyl compounds⁷ to produce the corresponding cyclopropane derivatives (eq 1) in preparatively useful yields (Table I). In a typical



α,β-Unsaturated carbonyl compound RCOCHN ₂		Cyclopropane derivative	Isolated yield, % ^a	<u>% trans</u> % cis	
H ₂ C=CHCOCH ₃	C6H2COCHN2	RC	80	6.0	
2 5	(CH _z) CCOCHN		79	4.9	
	EtOCOCHN ₂	COCH ₃	72	10	
H ₂ C=CHCOCH ₂ CH ₃	с ₆ н ₅ сосня ₂	RC COCH ₂ CH ₂	75 ^b	2.0	
Н ₂ С=СНСНО	C ₆ H ₅ COCHN ₂	PC-	70	1.3	
2	EtoCOCHN ₂	0 n _{CHO}	20	>10	
(CH ₃) ₂ C=CHCOCH ₃	C6H5COCHN2	RC (CH ₃) ₂	11	>10	

Table I.	Isolated Yield	ls and Isor	neric Compo	osition of	f Cyclopro	pane Deriv	atives	from A	ntimony
	Pentafluoride	Promoted H	Reactions	of α-Diazo	ocarbonyl	Compounds	with α ,	β-Unsa	turated
	Aldehvdes and	Ketones							

² Optimum yields were obtained with 1.5 molar equivalents of the α , β -unsaturated carbonyl compounds, except in reactions of ethyl diazoacetate with 3-buten-2-one (5 equiv.) and in reactions employing acrolein (10 equiv.). ^D After addition of α -diazoacetophenone at -78°C, the reaction solution was warmed to -45°C (30 min.).

procedure, antimony pentafluoride (2.0 mmol) was dissolved in 5 mL of freshly distilled methylene chloride under anhydrous conditions, cooled to $-78\,^{\circ}$ C, and then added to a dry ice/acetone cooled solution of 3-bussen 2-one (3.0 mmol) in 10 ml of methylene chloride. α -Diazoacetophenone (2.00 mmol) dissolved in 10 mL of methylene chloride was added dropwise over a 30 min period through a $-78\,^{\circ}$ C cooled condenser to the antimony pentafluoride - 3-buten-2-one solution. Gas evolution, which was monitored with a gas buret, occurred immediately upon addition and was generally complete upon termination of addition of the diazo ketone solution. Following complete gas evolution, 20 mL of 10% aqueous sodium hydroxide was added to the bright orange reaction solution followed by 100 mL of ether. The ether extract was washed with water and the organic solvent was evaporated to yield 1.6 mmol of 1-acety1-2-benzoylcyclopropane (80% yield). The yields of the *cis*- and *trans*-isomers (Table I) were determined by GLC analyses⁸ and the individual isomers were characterized from their singular spectral and physical properties.

When employed in amounts equivalent to the diazocarbonyl compound, antimony pentafluoride provided the optimum yields of cyclopropane derivatives among the Lewis acids that we have examined. The yield of 1-acety1-2-benzoylcyclopropane from the boron trifluoride etherate promoted reaction of α -diazoacetophenone with 3-buten-2-one at -78°C was less than half that obtained with antimony pentafluoride, and no improvement in yield could be obtained when the boron trifluoride etherate promoted reaction was performed at -15°C. Similar low yields of cyclopropane derivatives were observed in titanium tetrafluoride promoted reactions. Boron trifluoride and titanium tetrafluoride caused the production of significant amounts of α -fluoroacetophenone in cyclopropanation reactions with α -diazoacetophenone⁹ and, when ethyl ether was present in the reaction solution, α -ethoxyactophenone was produced. Triethyloxonium tetrafluoroborate, which has been successfully employed in ketone homologation reactions with ethyl diazoacetate⁶, was significantly less effective than even boron trifluoride etherate or titanium tetrafluoride.

The formation of cyclopropanes in such high yields is remarkable considering the expected operation of acid catalyzed homologation reactions, 6,10 particularly with aldehydes. Indeed, homologation products are observed in reactions of diazocarbonyl compounds with acrolein (predominantly hydrogen migration), but this process is significant only with ethyl diazoacetate. Diazo ketones have previously been reported to be unreactive towards ketones in intermolecular homologation reactions⁶; although homologation products are generally not evident from reactions that employ diazo ketones, particularly with vinyl alkyl ketones, such reactions do occur with aliphatic ketones under the reaction conditions that we have described. Ethyl diazoacetate is significantly more reactive than the diazo ketones that we have examined and, in reactions with α,β -unsaturated aldehydes and ketones, differentiates between cyclopropanation and homologation with less selectivity than do diazo ketones.

The results that we have obtained with mesityl oxide indicate that effective cyclopropanation of α,β -unsaturated carbonyl compounds may be limited by substituents on the vinyl group. Certainly ring closure will be subject to steric constraints due to substituents on the vinyl group; however, other factors may also account for the low yield of the cyclopropane product from reactions of α -diazoacetophenone with mesityl oxide, and further investigations of the scope and limitations of these reactions are underway. α,β -Unsaturated esters do not undergo cyclopropanation in reactions with diazo ketones in the presence of antimony pentafluoride and, as indicated by prior results from this laboratory,¹¹ α,β -unsaturated nitriles form vinyl oxazoles.

The isomeric trans/cis ratios of cyclopropane products reported in Table I are reproducible at constant temperature and at a constant molar ratio of the α , β -unsaturated carbonyl compound to diazocarbonyl compound. However, increasing the reaction temperature or increasing the molar ratio of unsaturated substrate to diazocarbonyl compound increases the relative yield of the less stable *cis*-isomer. That antimony pentafluoride could cause isomerization of the initially formed cyclopropane products was demonstrated by treating an isomeric mixture of 1-acety1-2-benzoy1cyclopropane (trans/cis = 4.6) with an equivalent amount of antimony pentafluoride at -78°C. This reaction was performed under the same reaction conditions as employed for cyclopropanation reactions but without 3-buten-2-one. Rapid isomerization to a trans/cis ratio of 12 occurred without measurable loss of 1-acety1-2-benzoy1cyclopropane. This result not only demonstrates that cyclopropylcarbonyl compounds are subject to acid catalyzed isomerization but, more importantly, suggests a convenient method for isomerization of cyclopropylcarbonyl compounds and, possibly, higher analogs of these systems without significant product loss due to structural rearrangement.¹²

Competition between cyclopropanation and homologation is mechanistically well formulated as 1,4- verses 1,2-addition of diazo compounds to Lewis acid - activated α,β -unsaturated carbonyl compounds. Although our preliminary results do not justify a complete mechanistic analysis for the cyclopropanation reaction, the data that we have obtained are consistent with the interpretation presented in Scheme I. Acid catalyzed isomerization of the initially formed cyclopropylcarbonyl compound occurs in the absence of excess unsaturated carbonyl substrate and provides Scheme I



a conveniently accessible route to 1,2-disubstituted cyclopropylcarbonyl compounds of high isomeric purity.

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