Synthesis and Thermal Rearrangement of Allylic 3,5,6-Trimethyl-2-Pyrazinylacetates: A Heterocyclic Carroll Rearrangement

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The synthesis of allylic 3,5,6-trimethyl-2-pyrazinylacetates **2-4** has been achieved by the reaction of 3,5,6-trimethyl-2-pyrazinylacetic acid lithium salt (**1**) with phenyl dichlorophosphate followed by addition of the allylic alcohol. On thermolysis, the allylic β-heteroaromatic esters underwent a rearrangement, analogous to the Carroll rearrangement, to generate the corresponding γ,δ-unsaturated heteroaromatic compound. The configuration of the double bond formed in the product was the *E*-isomer. The rate of the rearrangement was dependent on the substitution pattern of the allylic portion of the molecule with **4** > **2** > **3**. The ester enolate version of the heterocyclic Carroll rearrangement was investigated with **2**, however these conditions did not promote the rearrangement.

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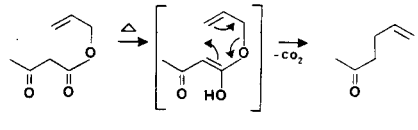
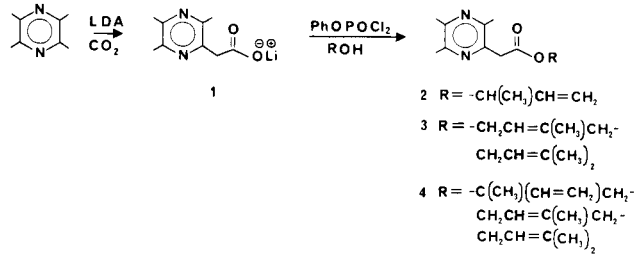
The Carroll rearrangement [1] has proven to be a useful thermal reaction to generate γ,δ-unsaturated ketones from allylic β-keto esters (Scheme I). It has been utilized on a commercial scale for the synthesis of geranyl acetone as well as β-ionone [2]. The Carroll rearrangement closely parallels the Claisen rearrangement [3], both of which have received renewed attention. This attention stems from the mild ester enolate conditions under which the rearrangement can occur [4,5].

We became interested in the Carroll rearrangement as a possible way to generate γ,δ-unsaturated pyrazines. Alkyl pyrazines, such as tetramethylpyrazine, can undergo alkylation [6] and aldol-type condensation [7] reactions, due to the enhanced activity of the alkyl group attached to the pyrazine nucleus. It was felt that this activity would allow allylic β-pyrazinyl esters to undergo a heterocyclic version of the Carroll rearrangement on thermolysis yielding the desired, γ,δ-unsaturated pyrazines. A literature survey failed to uncover any previous studies utilizing the Carroll rearrangement with allylic β-heteroaromatic esters. We now report on the synthesis of allylic 3,5,6-trimethyl-2-pyrazinylacetates and their thermal rearrangement.

Scheme I



Scheme II



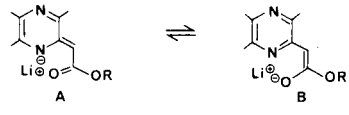
1

2 R = -CH(CH$_3$)CH=CH$_2$

3 R = -CH$_2$CH=C(CH$_3$)CH$_2$-CH$_2$CH=C(CH$_3$)$_2$

4 R = -C(CH$_3$)(CH=CH$_2$)CH$_2$-CH$_2$CH=C(CH$_3$)CH$_2$-CH$_2$CH=C(CH$_3$)$_2$

Scheme III



A B

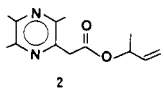
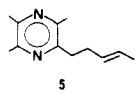
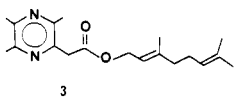
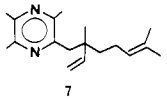
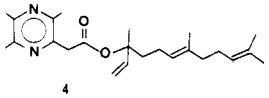
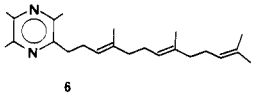
The synthesis of the allylic 3,5,6-trimethyl-2-pyrazinylacetates **2-4** was not as simple as expected. No reaction occurred when tetramethylpyrazine was reacted with lithium diisopropylamide (LDA) followed by an allylic chloroformate. However, the pyrazine anion did react with carbon dioxide to generate the stable carboxylate salt **1** in a quantitative yield. Various esterification methods utilizing the salt **1** were examined. The method which proved to be most effective essentialy utilized the procedure developed by Lui *et al.* [8] with only slight modifications (Scheme II).

In this reaction pyridine, phenyl dichlorophosphate, and the allylic alcohol were added to a solution of 3,5,6-trimethyl-2-pyrazinyl acetic acid lithium salt (**1**) in 1,2-dimethoxyethane at 0°. The resulting mixture was stirred at room temperature, under an atmosphere of nitrogen for approximately 18 hours, followed by extraction with chloroform and purification as described in the experimental section. This represented the first successful use of a lithium carboxylate salt in this reaction. In this study, we synthesized three allylic β-pyrazinyl esters **2-4** designed to examine the general scope of the reaction when the heteroaromatic moiety was a pyrazine nucleus.

The thermolysis of the allylic 3,5,6-trimethyl-2-pyrazinylacetates **2-4** was examined under a variety of conditions (Table I). The highest yield of heterocyclic Carroll rearrangement product resulted from thermolysis at 200° for 1 to 18 hours in diphenyl ether, with 2,6-di-*t*-butyl-4-methylphenol. The use of diphenyl ether [9] and 2,6-di-*t*-

Table I

Thermolysis of Allylic 3,5,6-Trimethyl-2-pyrazinylacetates

Substrate	Conditions [a]	Yield % [b]
 2	A	0
	B	24
	C	30
	D	46
	E	0
	F	0
 5		
 3	A	0
	D	10
 7		
 4	A	17
	D	Complex mixture
 6		

[a] Conditions: (A) 200°/1 hour/neat; (B) 200°/18 hours/neat; (C) 200°/18 hours/diphenyl ether; (D) 200°/18 hours/diphenyl ether/2,6-di-*t*-butyl-4-methylphenol; (E) 1 equivalent LDA/THF/−78 to 65°; (F) 2 equivalents LDA/THF/−78 to 65°. [b] Isolated yield of the product with identification by nmr, ir, and comparison with the authentic sample except for **7** [14].

butyl-4-methylphenol, a radical inhibitor, resulted in an increased yield of the rearrangement product by presumably suppressing side reactions and free radical processes which could occur on thermolysis.

The rate of the rearrangement was found to be dependent on the substitution pattern of the allylic portion of the molecule. In the examples studied, the rate of rearrangement of the tertiary allylic derivative **4** was greater than the secondary allylic derivative **2** which was greater than the primary derivative **3**. Our results are in accord with the generalizations seen in the Claisen rearrangement [10], as well as with the allylic acetoacetate derivatives [5]. Additionally, the primary derivative **3** was further influenced by the two γ substituents which would sterically hinder the rearrangement and resulted in a lower yield of the product **7**. An additional observation deserves mentioning. When the tertiary allylic derivative **4** was thermolyzed for 1 hour at 200° a 17% yield of the rearrangement product could be isolated however if **4** was thermolyzed for a longer period of time, 18 hours, only a complex mixture of products resulted. Thus, examining various rearrangement conditions is essential to optimize the yield of the heterocyclic Carroll rearrangement product.

The configuration [11-13] of the double bond formed in the product **5** was the *E* isomer as indicated by nmr and ir. It has been postulated [11] that the Carroll rearrangement occurs *via* a chair conformation in which a highly ordered six membered cyclic transition state accounts for the stereochemistry of the olefinic product. In the pyrazinyl system, a similar highly ordered transition state would be expected to account for the geometry of the double bond in the product.

The ester enolate version of the heterocyclic Carroll rearrangement [5] was investigated utilizing 3-buten-2-yl 3,5,6-trimethyl-2-pyrazinylacetate (**2**). When **2** was treated with one equivalent of LDA in THF and the temperature was varied from −78° to 65°, no reaction occurred. This result is analogous to the result obtained in the case of the allylic acetoacetate derivatives. A possible explanation is the exclusive formation of the enolate A, which does not equilibrate to the enolate B, and as a result, cannot rearrange under the reaction conditions (Scheme III). In the case of allylic acetoacetate derivatives, two equivalents of LDA would allow for the rearrangement to occur at 65° *via* a 1,3-dianion. In the pyrazinyl system no formally analogous dianion would be generated and as we observed, no reaction occurred when two equivalents of LDA were used.

In conclusion, the allylic 3,5,6-trimethyl-2-pyrazinylacetates have been shown to undergo the thermal heterocyclic Carroll rearrangement, in an analogous fashion to the allylic acetoacetate derivatives.

EXPERIMENTAL

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were recorded on a Perkin-Elmer 735B spectrophotometer. The chemical shifts and coupling constants (J) are reported in δ and Hertz respectively, using a Varian XL-300 or Bruker WP80 spectrometer, with TMS as the internal standard. Isocratic, normal phase high pressure liquid chromatography (hplc) was conducted with a Waters Associates Model 6000A equipped with a Partisil M20 10/15 column, solvent compositions are indicated for each application.

3,5,6-Trimethyl-2-pyrazinylacetic Acid Lithium Salt (**1**).

To a solution of 7.8 g (77.2 mmoles) of diisopropylamine in 50 ml of ether, under nitrogen and at 0°, was added 43.6 ml (77.2 mmoles) of 1.6*M* *n*-butyllithium in hexane. The solution was stirred at 0° for 15 minutes. To the solution of lithium diisopropylamide was added 10.0 g (73.5 mmoles) of tetramethylpyrazine in 100 ml of ether. The mixture was stirred for 30 minutes at 0° followed by addition of dry carbon dioxide gas. Carbon dioxide was bubbled through the mixture until the dark red mixture had turned into a yellow mixture, approximately 30 minutes. Immediately, the yellow precipitate was filtered, washed with cold ether, and dried under vacuum to yield 13.5 g (99%); ir (nujol mull): 1605 cm^{-1}; ^1H nmr (deuterium oxide): δ 3.67 (s, 2H), 2.48-2.17 (m, 9H).

3-Buten-2-yl 3,5,6-Trimethyl-2-pyrazinylacetate (**2**).

To a solution of 3,5,6-trimethyl-2-pyrazinylacetic acid lithium salt (1.0 g, 5.4 mmoles) in 25 ml of 1,2-dimethoxyethane at 0° were added sequentially pyridine (0.85 g, 10.8 mmoles), phenyl dichlorophosphate (1.71 g, 8.1 mmoles), and 3-buten-2-ol (0.78 g, 10.8 mmoles). The resulting mixture was stirred at room temperature under an atmosphere of nitrogen for approximately 18 hours. The mixture was poured into ice-water and extracted with chloroform. The combined chloroform extracts were washed with aqeuous saturated ammonium chloride followed by water, then dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure yielded a liquid which was purified by hplc (50% ethyl acetate/hexane) yielding 420 mg (33%) of **2** as an oil; ir (film): 1730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.1-5.37 (m, 1H), 5.35-5.05 (m, 3H), 3.82 (s, 2H), 2.48 (s, 9H), 1.32 (d, J = 6.0 Hz, 3H).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.65; H, 7.74; N, 11.95. Found: C, 66.43; H, 7.90; N, 11.77.

3,7-Dimethyl-2,6-octadien-1-yl 3,5,6-Trimethyl-2-pyrazinylacetate (**3**).

The synthesis of **3** was conducted on a 10.8 mmole scale using the conditions described for **2**. The liquid was purified by preparative thin layer chromatography on silica gel eluted with chloroform followed by ethyl acetate to yield 1.2 g (35%) of the product as an oil; ir (film): 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.28-5.00 (m, 2H), 4.62 (d, J = 7.0 Hz, 2H), 3.82 (s, 2H), 2.50 (s, 9H), 2.15-1.95 (m, 4H), 1.83-1.52 (m, 9H).

Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.27; H, 8.96; N, 8.68.

3,7,11-Trimethyl-1,6-10-dodecatrien-3-yl 3,5,6-Trimethyl-2-pyrazinylacetate (**4**).

The synthesis of **4** was conducted on a 5.4 mmole scale using the conditions described for **2**. The liquid was purified by hplc (40% ethyl acetate/hexane) to yield 1.0 g (50%) of the product as an oil; ir (film): 1730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.00 (dd, J = 10.0 Hz, 1H), 5.28-4.95 (m, 4H), 3.80 (s, 2H), 2.50 (s, 9H), 2.15-1.77 (m, 8H), 1.75-1.47 (m, 12H).

Anal. Calcd. for $C_{24}H_{36}N_2O_2$: C, 74.96; H, 9.44; N, 7.28. Found: C, 74.83; H, 9.40; N, 7.12.

Thermolysis of the Allylic 3,5,6-Trimethyl-2-pyrazinylacetates **2-4**.

A 95-105 mg sample of each of the allylic 3,5,6-trimethyl-2-pyrazinylacetates were thermolyzed in a glass tube under the specific conditions listed in Table I. The material was then purified by hplc (20% to 35% ethyl acetate/hexane). The products were identified by nmr, ir, and comparison with authentic samples [14].

2-(3-Pentenyl)-3,5,6-trimethylpyrazine (**5**).

To a solution of 1.13 ml (8.07 mmoles) of diisopropylamine in 20 ml of ether, under nitrogen and at 0°, was added 5.04 ml (8.07 mmoles) of 1.6*M* *n*-butyllithium in hexane. The solution was stirred at 0° for 15 minutes. To the solution of lithium diisopropylamide was added 1.0 g (7.34 mmoles) of tetramethylpyrazine in 10 ml of ether. The solution was stirred for 30 minutes at 0° followed by addition of 1.2 g (8.81 mmoles) of crotylbromide in 10 ml ether. This was stirred at 0° for 2 hours then 1 hour at room temperature. The mixture was quenched with aqueous saturated ammonium chloride and the ether layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure yielded a semisolid material which was purified by preparative thin layer chromatography on silica gel eluted with 10% ethyl acetate/hexane to yield 70 mg (5%) of the product as an oil; ir (film): 970 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.55-5.45 (m, 2H), 2.84-2.75 (m, 2H), 2.47 (s, 9H), 2.41-2.30 (m, 2H), 1.63 (d, J = 4.2 Hz, 3H).

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.59; H, 9.32; N, 14.51.

2-(4,8,12-Trimethyl-3,7,11-tridecatrienyl)-3,5,6-trimethylpyrazine (**6**).

The synthesis of **6** was conducted on a 14.7 mmole scale using the conditions described for **5**. The liquid was purified by preparative thin layer chromatography on silica gel eluted with 10% ethyl acetate/hexane to yield 3.1 g (65%) of the product as an oil; ir (film): 980 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.19 (t, J = 7.3 Hz, 1H), 5.14-5.05 (m, 2H), 2.82-2.71 (m, 2H), 2.48 (s, 9H), 2.39 (dd, J = 7.3 Hz, 2H), 2.13-1.92 (m, 8H), 1.68 (s, 6H), 1.60 (s, 3H), 1.56 (s, 3H).

Anal. Calcd. for $C_{23}H_{36}N_2$: C, 81.10; H, 10.67; N, 8.23. Found: C, 80.71; H, 10.57; N, 8.14.

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[14] The only exception is pyrazine **7** which was identified by gc/ms. Mass spectrum, m/e 273 (molecular ion + 1).