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AN ISOSTERIC SUBSTITUTION REACTION OF SUBSTITUTED IMIDAZOLIDINETHIONES

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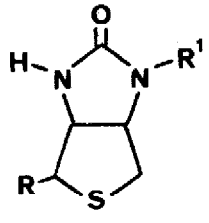
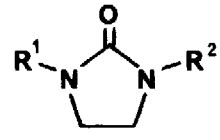
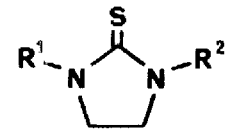
In naturally occurring systems, biotin (1a) functions as an important carbon dioxide transfer reagent.[1] The overall enzymic process proceeds with carboxylation usually occurring at an activated position on the biological substrate. In relation to a current project dealing with the mechanism of biotin catalysis,[2] it was of interest to examine the reaction of ketenes with a series of acyl substituted imidazolidones (2a-2d)[3-6] and imidazolidinethiones (3a-3d).[2,6,7] These substrates can be considered as potential model compounds for the suggested key intermediate 1b in these trans-



1a $R^1 = H$
b $R^1 = CO_2^-$

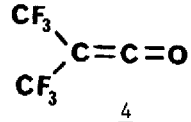


2a $R^1 = H$, $R^2 = COCH_3$
b $R^1 = H$, $R^2 = CO_2CH_3$
c $R^1 = CH_3$, $R^2 = COCH_3$
d $R^1 = CH_3$, $R^2 = CO_2CH_3$



3a $R^1 = H$, $R^2 = COCH_3$
b $R^1 = H$, $R^2 = CO_2CH_3$
c $R^1 = CH_3$, $R^2 = COCH_3$
d $R^1 = CH_3$, $R^2 = CO_2CH_3$

formations. In this communication we wish to report the results obtained for the reaction of compounds 2a-2d and 3a-3d with the highly reactive bis(trifluoromethyl)ketene (4).[8]



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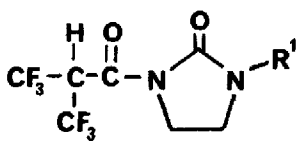
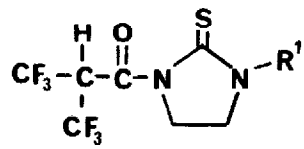
Treatment of the N-H substituted imidazolidones (2a,2b)[3,4] and imidazolidinethiones (3a,3b)[7,2] in dichloromethane with 1.1 equivalents of 4 gave the expected N-α-H-hexafluoroisobutyryl adducts 5a, 5b, 6a and 6b in good yields.[9,10] The ^{1}H-NMR for these adducts showed a characteristic septet (J=7.5 Hz) for the lone methine proton.[8] The observed products can be explained in terms of

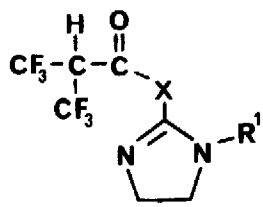


5a $R^1 = COCH_3$
b $R^1 = CO_2CH_3$



6a $R^1 = COCH_3$
b $R^1 = CO_2CH_3$

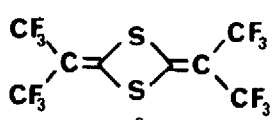
addition of 4 occurring either directly at the ring nitrogen atom or at the carbonyl or thione group of the starting material. The latter mechanism initially gives the isomeric imidazoline 7. However, rearrangement of 7 to either 5 or 6 should occur rapidly.[11]



7 (X = O, S)

Addition of the ketene 4 to a dichloromethane solution containing the imidazolidones 2c[5] and 2d[6] under similar conditions led to the total recovery of starting urea in each case. The same results were observed in dimethoxyethane and dimethylformamide and at elevated temperatures (60 → 130 °C).

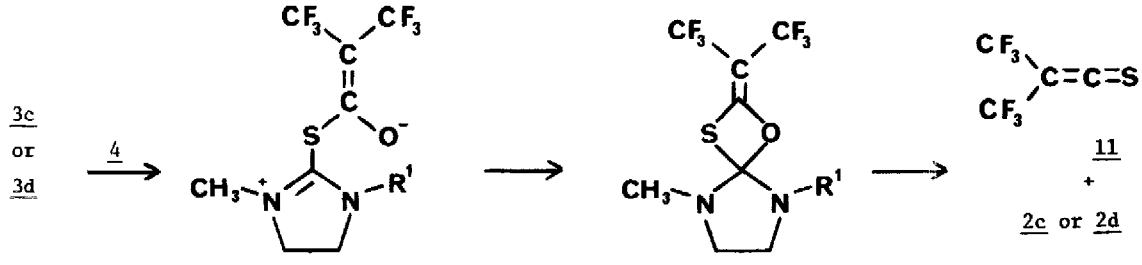
When, however, the N,N'-disubstituted imidazolidinethiones 3c[6] and 3d[6] were treated with 4 under identical experimental conditions, the corresponding oxygen analogs 2c[5] and 2d[6] were obtained in quantitative yield along with 2,4-bis[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane (8).[12,13]



8

The formation of 2c and 2d in these last experiments can be envisioned to occur by initial attack of ketene 4 by the imidazolidinethione (3c or 3d) to give zwitterion 9a and 9b, respectively. Intermediate formation of the oxathietane ring 10 in the subsequent step, followed by ring fragmentation would generate the observed products and 11. Bis(trifluoromethyl)thioketene (11) is

known to dimerize to 8 in the presence of nitrogen, oxygen, and sulfur nucleophiles.[12] In an analogous fashion, reaction of either 2c or 2d with ketene 4 would lead to the intermediate formation of a 1,3-dioxetane ring. However, fragmentation of this adduct in either direction leads to the regeneration of both starting materials. The appropriate labeling experiment needed to test this possibility, however, has not been conducted.



9a $R^1 = COCH_3$
b $R^1 = CO_2CH_3$

10a $R^1 = COCH_3$
b $R^1 = CO_2CH_3$

Isolated examples of isosteric replacement reactions have been observed in the past.[12,15-19] Notable cases are the conversion of amides and ureas to thioamides[15] and thioureas[16] with phosphorous pentasulfide, the sulfur-oxygen exchange between isothiocyanate and isocyanate esters,[17,18] and the reaction of 11 with electron-rich carbonyl compounds to give 4 and the dithietane adduct of 11 and the corresponding thione.[12] Analogously, 1,3-oxathietane rings have been suggested as intermediates in the last two isosteric substitution reactions.[12]

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References and Notes

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9. All the reactions were carried out in sealed tubes at 65 °C for 48 hours unless otherwise noted. Removal of the volatiles followed by vacuum distillation or recrystallization gave the observed products.

10. Satisfactory infrared, pmr, mass spectra and elemental analyses were obtained for all new compounds described herein.

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13. The isosteric substitution reaction observed in this study appears to be a general reaction for thioureas and similarly substituted thiones with ketene 4.[14] Treatment of N-carbomethoxy-N'-diphenylacetylimidazolidinethione, 1,3-diethyl-2-thiobarbituric acid and N-methylbenzothiazole-2-thione with 4 led to an analogous replacement of the sulfur of the thione group to an oxygen atom (99, 43 and 30 percent yields, respectively). However, addition of ketene 4 to ethylenetrithiocarbonate, 3-ethyl-2-thioxo-4-oxazolidinone and thiobenzophenone under identical conditions[9] led to the recovery of the starting thione in each case.

14. The S→O heteroatom interchange reaction reported herein did not occur with ketene (chloroform, 22 °C, 1 hour) and dichloroketene (dimethylformamide, -30 °C, 3 hours).

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