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N→C ESTER TRANSFER IN N-CARBOXYLIC ACID ESTER DERIVATIVES OF 2-MERCAPTOBENZIMIDAZOLE
A MODEL REACTION FOR BIOTIN-PROMOTED TRANSCARBOXYLATIONS

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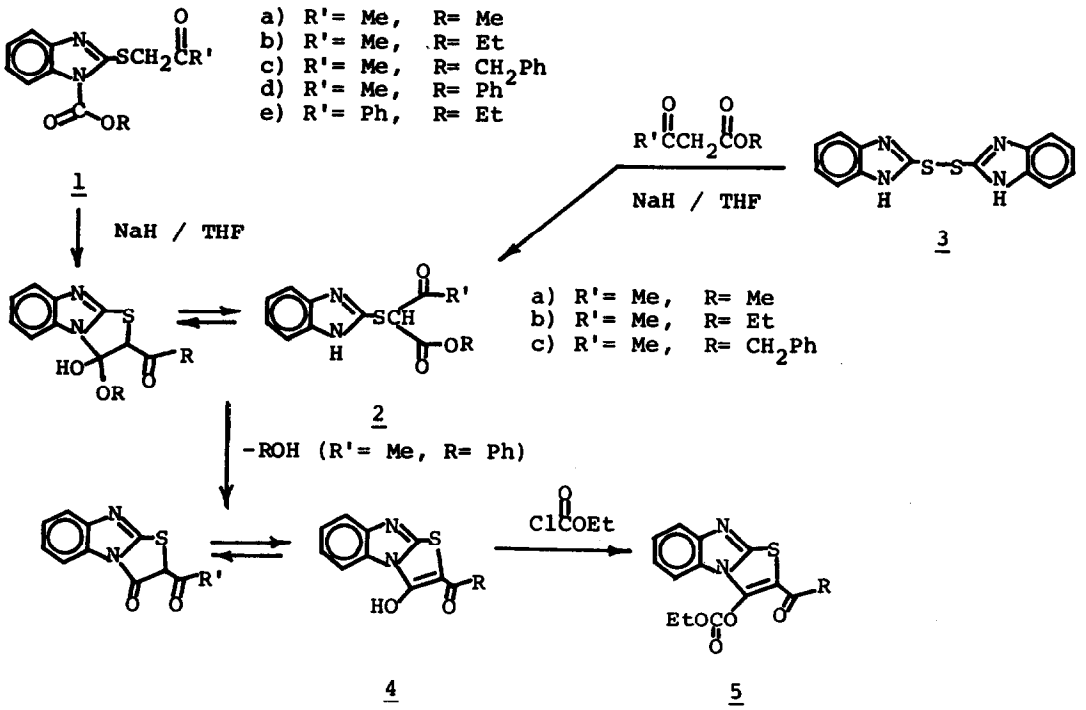
It has been well established that carboxybiotin-enzyme transfers a carboxyl group to an acceptor by biotin dependent transcarboxylase.[1] In this transformation, 1'-N-carboxylated biotin and O-carboxylated biotin have been suggested for the active form of coenzyme.[2] However, the attempts to transfer a carbon dioxide moiety from carboxybiotin analogues to suitable model compounds have met with little success.[3] In all cases studied, these unsatisfactory results would be attributed to the low electrophilicity of N-carboxyl group to an acceptor.

Recently, we have reported the first example of intramolecular acyl migrations between neutral nitrogen atom and neutral carbon atom in N-acyl derivatives of 2-mercaptobenzimidazole under the mild conditions.[4] From these findings, it occurred to us that the reactivity of nitrogen bound-CO_2 moiety would be enhanced if CO_2 moiety and a nucleophilic acceptor are properly jaxtaposed. We now report a facile N→C ester transfer with organic base catalyst in model studies on transcarboxylation of carboxybiotin intermediate derived from N-carboxylic acid ester derivatives of 2-mercaptobenzimidazole.

A variety of N-carboxylic acid esters (1),[5,6] model compounds for N-carboxybiotin, were synthesized from corresponding chloroformates and S-acetonyl- or S-phenacyl-2-mercaptobenzimidazole with sodium acetate in tetrahydrofuran. Firstly, we found that three types of reactions take place in the intramolecular migrations of N-ester group of 1 to the carbanion of thiomethylene group formed with sodium hydride. When S-acetonyl-N-ethoxycarbonyl-2-mercaptobenzimidazole (1b) was treated with sodium hydride at room temperature, ethyl 2-acetyl-2-(2'-benzimidazolylthio)-acetate (2b)[6] was obtained in 94% yield, which was identical with an authentic sample prepared from di-2-benzimidazolyl disulfide (3) with ethyl acetoacetate in the presence of sodium hydride:[7] m.p. 149-151°; ir (ν, KBr) 3100-2500(broad), 1640(C=O), 1590(C=O) cm^{-1}; nmr(δ, $CDCl_3$) 1.17, 1.33 (t, total 3H), 2.20, 2.38(s, total 3H), 4.18, 4.30(q, total 2H), 4.92(s, 1H) and 6.92-7.70(m, 4H). The same ester transfer reaction occurred in compounds

1a and 1c which afforded 2a and 2c,[6,8] respectively. On the other hand, the reaction of 1d with sodium hydride did not yield an expected product 2d, but 4,[9] which was confirmed by forming 5[6] from 4 and excess ethyl chloroformate (Scheme 1): m.p. 173-177°(decomp.); ir(ν, KBr) 1770, 1680(C=O) cm^{-1}; nmr(δ, $CDCl_3$) 1.63(t, 3H), 2.60(s, 3H), 4.70(q, 4H) and 7.50-8.50(m, 4H).

Scheme 1



1 2 3 4 5

An alternative preparation of 2d was unsuccessful: the reaction of 3 with phenyl acetoacetate in the presence of sodium hydride gave 4 in 90% yield. However, this fact shows that 2d is implied as an intermediate of 1d with sodium hydride. The third type of transesterification to an anionic site was observed in the case of 1e, which gave ethyl benzoylacetate in 88% yield, which is also implied to be formed through 2e, though the mechanism of its formation has not been clarified in detail.[10] In each reaction mentioned above, ester transferred product of 2 is commonly involved in the reaction process, which denotes that the ester transfer reaction induced with carbanion may take place in each model compound 1.

Then we tried to induce the ester transfer reaction with organic base catalysts such as 1,5-diazabicyclo-[4.3.0]-5-nonene(DBN) or triethylene diamine (TED) and found that the normal intramolecular transesterifications take place similarly with 1a-1c. When compound 1c was treated with equimolar amount of

DBN or TED at room temperature for 24 hr, crystalline 2c was isolated in the yield of 55% and 34%, respectively. Furthermore, the catalysis of DBN on the transesterification of 1a into 2a was examined: the ratios of 2a vs 1a were determined from nmr spectra of the reaction mixture by comparing the integrals of peaks characteristic of 1a and 2a.[11] The results are shown in Table I.

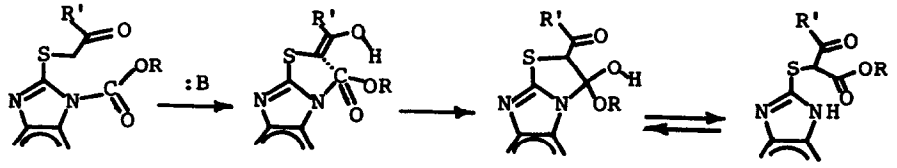
Table I N→C ester transfer of compound 1a with DBN at room temperature in tetrahydrofuran.

DBN, mol%	2a, %	1a, %
14.0	43	57
9.9	36	64

Consequently, the data indicate that facile N→C ester transfer takes place under mild conditions with catalytic amounts of organic bases such as DBN or TED.

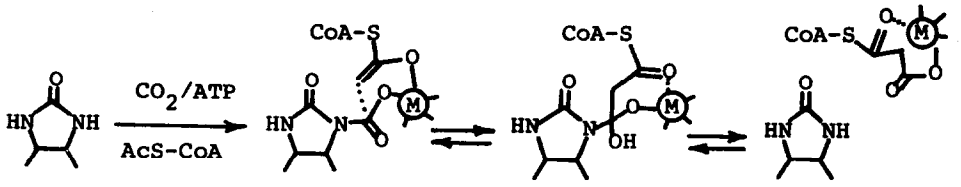
Although the detailed mechanism of the reaction is not clarified yet, a cyclic carbinolamine 7[12] may play an important role in this N→C ester transfer reaction, as shown in Scheme 2.

Scheme 2



1 7 2

Scheme 3



8 9

It is noteworthy that neither the reverse C→N acyl transfer nor C→N ester transfer was observed in the experiment starting with 2a. The intermediary carbinolamine 7 can reasonably be anticipated from nmr data[11] and from the fact of isolating 4 as shown in Scheme 1.

It has been shown that esters of N-carboxy-2-imidazolidone are inactive

toward C-N bond cleavage by nucleophilic attack.[3] Recently, an independent study on the intramolecular transesterification of N-methyl-N'-carbomethoxy-2-phenacylthioimidazolinium fluoroborate (10) has been reported by Kohn, who proposed that the ester transfer reaction of 10 appeared to be facilitated by the presence of a positive charge on the imidazoline ring.[13] Our results show that similar ester transfer reactions do occur in our model compound 1 as described above, even in the absence of a positive charge on the imidazole ring using organic base catalysts. From these facts, it is suggested that transcarboxylation from carboxybiotin would occur, if the interacting functional groups are appropriately jaxtaposed as shown in Scheme 3 to form the carbinolamine-like intermediate 9 from 8.

References

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3) a) M. Caplow, J. Amer. Chem. Soc., 87, 5774 (1965); M. Caplow and M. Yager, ibid., 89, 4513 (1967); b) H.J. Shaeffer and P.S. Bhargava, J. Pharm. Sci., 51, 1116 (1962); 53, 137 (1964).
4) Y. Akasaki and A. Ohno, J. Amer. Chem. Soc. 96, 1957 (1974).
5) Yields and melting points of 1 are as follows: 1a; 84%, 97-99°, 1b; 90%, 100-103°, 1c; 85%, 108-110°, 1d; 95%, 127-129°, 1e; 95%, 129-131°.
6) Satisfactory elemental analyses were obtained for all compounds.
7) T. Fujisawa, K. Hata and T. Kojima, Chem. Lett., 287 (1973).
8) 2a: m.p. 155-157°; ir(ν, KBr) 1650(C=O), 1590(C=O) cm^{-1}; 2c: m.p. 125-127°; ir(ν, KBr) 1630(C=O), 1590(C=O) cm^{-1}.
9) This compound is sparingly soluble in most organic solvents: m.p. 197-199° (decomp.), Mass; m/e 232(M^+).
10) Similar behavior has been found in the reaction of 1-acetyl-2-phenacylthiomethyl-benzimidazole with sodium hydride. In this case, N→C acyl migration product of 1-phenyl-2-(2'-benzimidazolylmethylthio)-butane-1,3-dione is involved as an intermediate. Y. Akasaki and M. Fukuyama will soon report the results elsewhere.
11) The nmr signal for methoxy proton of 1a appeared at δ 4.43, whereas, 2a has four signals due to methoxy protons, δ 4.06, 4.10, 4.11 and 4.13(total 3H). This indicates that 2a, carbinolamine 7a and their enol forms are equilibrated in DMSO-d_6.
12) In the case of N-acyl derivatives of 2-mercaptobenzimidazole, carbinolamine intermediate was trapped from the reaction mixture by ethyl chloroformate. See ref. 4.
13) H. Kohn, J. Amer. Chem. Soc., 98, 3690 (1976).