Tetrahedron Letters No. 52, pp 5011 - 5014. 0040-4039/79/1222-5011$02.00/0

REACTION OF N,N'-CARBONYLDIIMIDAZOLE AND N,N'-THIONYLDIIMIDAZOLE WITH CARBONYL COMPOUNDS: A NEW IMIDAZOLE TRANSFER REACTION

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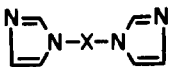
Summary: Ketones and aldehydes undergo facile addition reaction with N,N'-thionyldiimidazole to give the monoimidazole and the diimidazole.

N,N'-Carbonyldiimidazole (1a) is a member of a new class of compounds with a wide synthetic potential.[1] In spite of its utility as a carbonyl transfer reagent,[2] the imidazole transfer reaction[3] using 1a has not been fully explored. And also, although the thionyl transfer reaction[4] using N,N'-thionyldiimidazole (1b) and the thiocarbonyl transfer reaction[5] using N,N'-thiocarbonyldiimidazole (1c) are well known, little attention has been paid to the imidazole transfer reaction using these reagents (1b, c). Our particular interest was focused on the imidazole transfer reaction using 1a-c in connection with the methodology for N-alkylation of imidazole and the synthesis of antimycotic imidazoles.[6] We report here a new imidazole transfer reaction based on the reaction of 1a, b with carbonyl compounds.[7]



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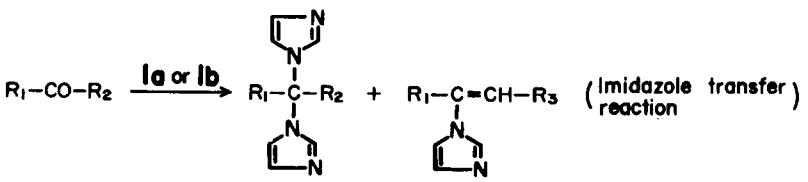
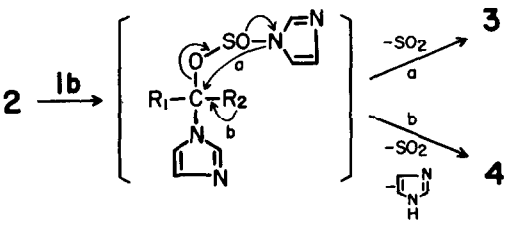
a: X=CO
b: X=SO
c: X=CS
d: X=SO_2

The reaction of 1b (1.5 mol eq.) which is formed in situ, and acetophenone (2a) at room temperature in dichloromethane afforded the diimidazole (3a) and the monoimidazole (4a), which were characterized by elemental analysis and ^{1}H NMR.[8] Elevated temperature did not improve the product yield. When 2a was allowed to react with 1a, or 1c, no reaction product formed and the starting material was recovered. Similarly, in the case of the reaction of N,N'-sulfuryl-



2 3 4

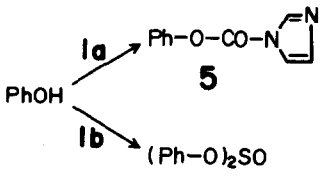
diimidazole (1d) with 2a, no reaction product was obtained. The conversion of 3a into 4a under various conditions was examined with the hope that transformation would occur. Treatment of 3a with sodium hydride in dimethylformamide or aqueous hydrochloric acid resulted in the recovery of the starting material.



Consideration of the formation of the two products (3a and 4a) suggested a plausible mechanism involving initial nucleophilic addition of 1b to the carbonyl group followed by elimination of sulfur dioxide and imidazole to yield 3 and 4. The facile conversion of R-O-SO-imidazole into R-imidazole and sulfur dioxide is well recognized.[1] With this mechanistic consideration in mind, the reaction of 1b with a variety of substituted acetophenones (2b-e) was examined. Representative results are summarized in Table I.

p-Methoxyacetophenone (2b) and p-nitroacetophenone (2c) showed sharply contrasting reaction periods and product ratios (3b, c and 4b, c), indicating that electron-attracting substituents promote the addition reaction and the elimination of sulfur dioxide and imidazole to give the monoimidazole (4). The same results were found for benzophenones, namely treatment of benzophenone or p-methoxybenzophenone with 1b resulted in the recovery of starting materials, although p-nitrobenzophenone (2f) gave the diimidazole (3f). 2-Benzoylpyridine (2g) gave the diimidazole (3g) under similar conditions.

Aliphatic ketones such as acetone (2h), and cyclohexanone (2i) reacted with 1b to give the diimidazole (3h and 3i) and the monoimidazole (4h and 4i) in similar ratios,[9] respectively, at relatively lower yields. Aliphatic aldehydes such as β-phenylpropionaldehyde, and n-capronaldehyde gave no clearly distinguishable product under similar conditions.



Phenol is known to react with 1a or 1b to give imidazole N-carboxylic acid phenylester (5)[1,10] or sulfurous acid diphenylester (6),[1,4a] respectively.

When carbonyl groups were situated in phenyl ring, the phenolic OH group did not react with 1a or 1b. Namely, treatment of ethyl salicylate or p-hydroxybenzophenone with 1b resulted in recovery of the starting materials. These results prompted us to examine the reaction of o-hydroxy aroyl compounds (2m-o) with 1a or 1b. In contrast to the complete inertness of benzo-

Table I. Reactions of 1a, b with Carbonyl Compounds (2)

	R_1	R_2	R_3	Reaction time[b] (hr)	Yield (%)[a] 2[c]	3	4
a	Ph	Me	H	96	14	37	12
b	p-MeO-Ph	Me	H	96	19	49	2
c	p-NO_2-Ph	Me	H	19		26	33
d	p-Me-Phe	Me	H	96	23	32	7
e	p-Cl-Ph	Me	H	96	12	26	13
f	p-NO_2-Ph	Ph		48	80	13	
g	α-Pyridyl	Ph		48	20	57	
h	Me	Me	H	0.5		26	4
i	R_1-R_2; $-(CH_2)_5-$	R_1-R_3; $-(CH_2)_4-$		1		20	9
j	Ph	H		2		30	
k	α-Pyridyl	H		0.25		57	
l	α-Furyl	H		0.5		26	
m	o-OH-Ph	Ph	H	1.5 21[d]	 31[d]	82 37[d]	
n	o-OH-Ph	Me	H	1 4.5[d]	 17[d]		94 31
o	o-OH-Ph	H	H	0.5 0.5[d]		39 15[d]	
p	p-OH-Ph	Me	H	96		11	3
q	o-MeO-Ph	Me	H	96	15	34	13
r	o-NH_2-Ph	Me	H	0.5	3	17	37

[a] No attempt was made to obtain maximum yields. The % represents the yields isolated. [b] At room temperature. Using an 1.5-fold excess of 1b. [c] recovery of starting material. [d] Using an 1.5-fold excess of 1a instead of 1b.

phenone towards 1b, o-hydroxybenzophenone (2m) reacted smoothly with 1b, forming the diimidazole (3m) in good yield. o-Hydroxyacetophenone (2n) also underwent rapid reaction with 1b to give the monoimidazole (4n) in good yield. And interestingly, 1a[11] also reacted with 2m and 2n to give 3m and 3n, respectively. Similar results were obtained for the reaction of benzaldehydes, namely, when 2j was allowed to react with 1a, no reaction product was obtained, and the starting material was recovered. On the other hand, salicylaldehyde (2o) reacted with 1a to give the diimidazole (3o). The above facile reaction attributed to the ortho OH group was not observed for the reaction of p-hydroxy (2p) or o-methoxyacetophenone (2g). These results clearly indicate the importance of internal hydrogen bonding between the carbonyl and the phenolic hydroxy groups for the reactivity of these carbonyl compounds, in lowering the energy of the transition state for the addition of 1a, b to the carbonyl group.[12] From the comparison of the reaction of 2a and 2r, we can reasonably conclude that the contribution of the NH_2 group

in the ortho position due to internal hydrogen bonding lead to the facile reaction.

The present methodology and development suggest that the imidazole transfer reaction may occur with many other functional groups[7] with the action of the appropriate diimidazolide (1). Investigations are continuing on the extension and application of the procedure reported here.

REFERENCES AND NOTES

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(2) (a) J. P. Kutney and A. H. Ratcliffe, Synthetic. Commun. 5, 47 (1975); (b) H. G. Heine, H. H. Fischer and D. Wendisch, Tetrahedron 29, 2333 (1973). The term "Carbonyl transfer reaction" is used in a sense analogous to "thiocarbonyl transfer reaction[5c]".

(3) We propose the use of the term "imidazole transfer reaction" in comparison with "thiocarbonyl transfer reaction[5c]": The conversion of triphenylcarbinol into triphenylmethyl imidazole using 1a, b seems to be an example of the imidazole transfer reaction: see K. H. Buchel, W. Draber, E. Regal, and M. Plempel, Arzneim. Forsch. 22, 1260 (1972).

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(7) For the preceding paper of this series, see M. Ogata, H. Matsumoto, and S. Kida, "Reaction of N,N'-carbonyldiimidazole and N,N'-Thionyldiimidazole with Amides: an Imidazole Transfer Reaction", Heterocycles, in press.

(8) 3a: Mp 141-143 °C, NMR ($CDCl_3$) δ [2.60 (s, 3H, Me), 6.83-7.47 (m, 11H, aromatic)]. 4a: liquid, (monopicrate: mp 113-115.5 °C), IR (neat) 1638 cm^{-1}; NMR ($CDCl_3$) δ [5.33 (broad s, 2H, $=\!\!<^{H}_{H}$), 7.05-7.67 (m, 8H, aromatic)].

(9) (a) It seems that the enol form of the carbonyl substrates does not take part in this reaction, namely, the reaction of 1b with acetone (2h) and cyclohexanone (2i) which has a different enol percent (reference 9b) gave the diimidazole (3h and 3i) and the monoimidazole (4b and 4i) in similar yields, respectively. (b) For enolization of ketones (Percent enol in the liquid), Acetone (2.5×10^{-4}), and cyclohexanone (2.0×10^{-2}): G. Schwarzenbach and Ch. Wittwer, Helv. Chim. Acta 30, 669 (1947). G. S. Hammond, in "Steric Effect in Organic Chemistry", M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N.Y., 1956, p 445.

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(11) The greater reactivity of 1b compared to that of 1a is described in reference 1.

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(Received in Japan 17 September 1979)