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SYNTHESIS OF A NON-SYMMETRIC AZODICARBONYL COMPOUND AND ITS REGIOSELECTIVE REACTION WITH ORGANOMETALLIC REAGENTS

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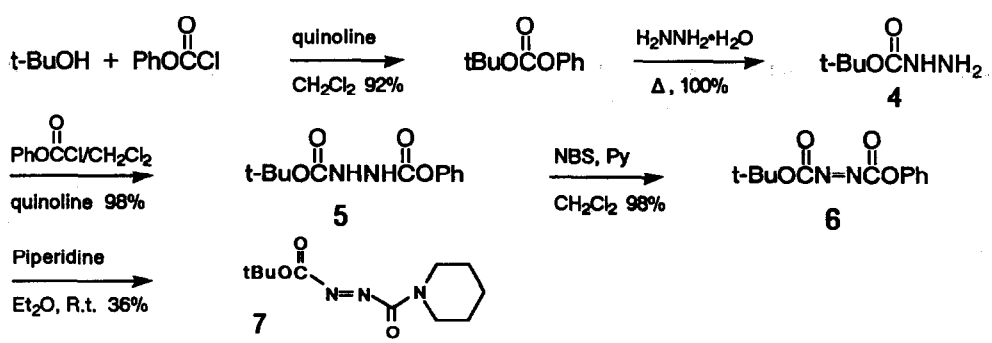
The non-symmetric azodicarbonyl compound 7 reacted with R-M/Lewis acid regioselectively at the nitrogen atom attached to the amide group giving 9, whereas it reacted with R-M at the nitrogen atom attached to the ester group producing 8 in high yield.

1,1'-Azodicarbonyl compounds (1) such as di-t-butylazodicarboxylate (DBAD) and diethylazodicarboxylate (DEAD) are synthetically useful nitrogen electrophiles. The reactivity of those compounds toward a carbon nucleophile is similar to the C=C (2) or C=N (3) analogue.[1] Until now symmetrical azodicarbonyl compounds

GWE-N=N-EWG (1) GWE-C=C-EWG (2) GWE-C=N-EWG (3)

have been used, except for one case,[2] for the synthesis of amine and amino acid derivatives, since (i) the discrimination of the two nitrogen atoms is not necessary, and (ii) only one of two nitrogen atoms is useful in the final stage of the amino acid synthesis.[1] However, a non-symmetric azodicarbonyl compound also becomes an important nitrogen electrophile for the following reasons. (1) When an azodicarbonyl compound acts as a 4π component in a certain Diels-Alder reaction, the regioselectivity on two carbonyl groups becomes an important problem.[3] (2) When a chiral auxiliary is introduced in the EWG group, a non-symmetric system as well as a symmetric chiral azo compound becomes useful to achieve high asymmetric induction.[4]

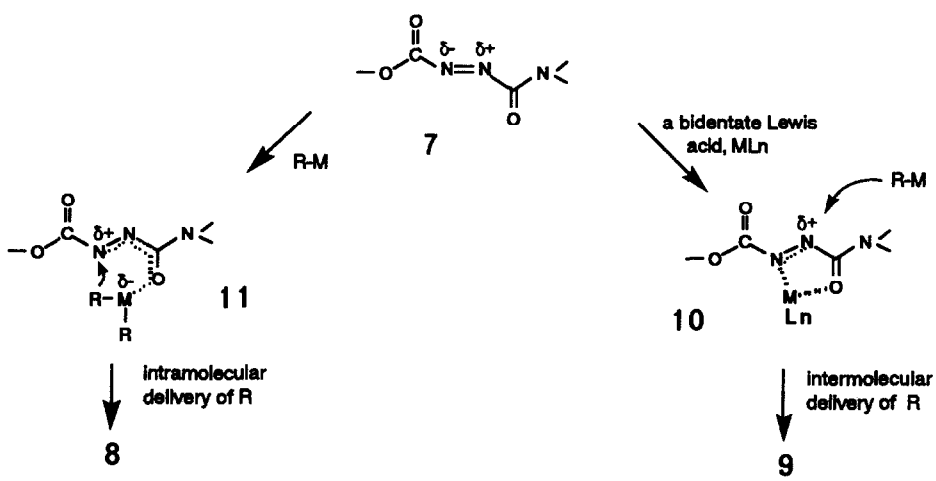
We report the synthesis of the ester-amide substituted system **1a** (EWG=CO_2tBu and CON<), and its regioselective reaction with organometallic compounds. t-Butyl carbazate **4** was prepared from t-butyl phenyl carbonate in high yield, which was synthesized by the reaction of phenyl chloroformate with t-butyl alcohol.[5] The condensation between **4** and phenyl chloroformate took place in the presence of quinoline, giving t-butyl phenyl hydrazodiformate **5** in 98% yield. Treatment of **5** with NBS in pyridine[6] gave t-butyl phenyl



azodiformate 6 in 98% yield. The selective substitution of the phenoxy group with piperidine took place at room temperature, producing 7 in 36% yield.[7] The use of the t-BuO and PhO substituents is important for the preparation of 7, since diphenoxyazodicarboxylate gave the disubstitution product upon treatment with piperidine. The reaction of 7 with various organometallic reagents is summarized in Table 1. The structure of the regioisomers was determined as follows. The t-butoxycarbonyl group was selectively deprotected by TFA-CH_2Cl_2 (1:1) at room temperature, and the resulting product was analyzed by ^1H NMR spectroscopy. The -CHN proton of R group in 8 shifted to higher fields by ~1 ppm, whereas the corresponding proton in 9 did not move at all or moved to lower field very slightly (<~0.02 ppm).

Very interestingly, the Lewis acid mediated reaction gave 9 exclusively irrespective of the reagent type (entries 3-6), whereas the reaction of the zinc and aluminum reagents in the absence of Lewis acids produced 8 exclusively (entries 1, 7, and 8). The similar tendency was observed in other cases, although the selectivity is not so high (entry 2, 9, 10, 12, and 13). For the synthesis of 8, trialkylaluminum and dialkylzinc reagents gave the best result. $R_2Zn/TiCl_4$, $R_4Pb/TiCl_4$, and allylic tin/$ZnCl_2$ were useful for the synthesis of 9.

A marked contrast of the regioselectivity can be understood in terms of the following chelation mechanism. An ester group is stronger electron withdrawing substituent than an amide, and thus the nitrogen atoms of 7 must be polarized as shown in Scheme 1. Accordingly, the conjugate addition of R-M to the -N=N-CO- system

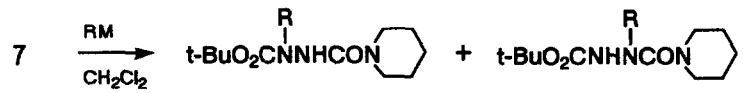


Scheme 1. Regioselective Reaction of 7

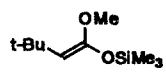
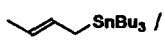
takes place in an intramolecular manner (11), giving 8 regioselectively. If a bidentate Lewis acid is added prior to the addition of R-M, the five membered chelation intermediate 10 would be formed. R-M must react at the nitrogen atom bearing δ+ charge, producing 9 exclusively.[8]

We are now in a position to prepare various kind of ester-amide mixed azodicarbonyl compounds. Introduction of a chiral auxiliary to either the amide or ester substituent is possible. The present finding on the regiocontrol may be useful for such an asymmetric reaction.

Table 1. Reaction of 7 with various organometallic reagents.[a]



8 9

Entry	RM	Temp (°C)	Reaction time, h	Product ratio 8 : 9	Total isolated yield, %
1	Et_2Zn	-78	1	>98 : -	87 (3)[b]
2	EtZnCl	-78	1	90 : 10	91 (5)[b]
3	$Et_2Zn/TiCl_4$	-78	1	- : >98	64 (5)[b]
4	 / $TiCl_4$	-78 → r.t.	12.5	- : >98	15[c]
5	 / $ZnCl_2 \cdot OEt_2$	-78 → r.t.	2	- : >98	73[d]
6	$Et_4Pb/TiCl_4$	-78	0.7	- : >98	61 (6)[b]
7	Et_3Al	-78	4	>98 : -	94
8	Et_2AlCl	-78	1	>98 : -	~100
9	$Et_3Al/TiCl_4$	-78 → -30	2	53 : 47	80
10	Et_3B	reflux	3.5	49 : 51	71 (28)[b]
11	$Et_3B/ZnCl_2 \cdot OEt_2$	-78 → r.t.	5	- : >98	38 (24)[b]
12	BuLi[e]	-78 → r.t.	2	74 : 26	88 (8)[b]
13	$Bu_2CuLi \cdot BF_3 \cdot OEt_2$[e]	-78 → r.t.	4	35 : 65	62 (28)[b]

[a]Product ratio was determined by 270MHz ^1H NMR. [b]The reduction product, $tBuO_2CNHNHCON$⟨⟩, was formed as a by-product. [c]The starting material was recovered considerably. [d]Crotyltin reacted predominantly at the γ-position, but the α-product was also obtained in 7% yield. [e]Ether was used as a solvent.

References and notes

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4) A certain non-symmetric chiral system produced higher ee than the corresponding symmetric system, and the result will be reported shortly.
5) L. A. Carpino, B. A. Carpino, C. A. Giza, R. W. Murray, A. A. Santilli, P. H. Terry, Org. Syn. Coll., Vol.V, p.168 (1973).
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7) A Michael type addition of piperidine to the N=N double bond of **6** (and **7**) took place as a side reaction, leading to the relatively low yield of **7** (E. E. Smissman, A. Makriyannis, J. Org. Chem., **38**, 1652 (1973)). The substitution of the t-butoxy group or disubstitution reaction did not occur.
8) $Et_3Al/TiCl_4$ produced a mixture of **8** and **9** (entry 9, Table 1). Presumably, the transmetallation of the aluminum reagent to the titanium reagent competes with the chelation mechanism, resulting in the low regioselectivity.

[General procedure for the preparation of 8]

To a CH_2Cl_2 solution (4 ml) of **7** (0.5 mmol, 120 mg), cooled at -78°C, was added a hexane solution of the organometallic reagent (0.55 mmol). The reaction was monitored by TLC. When **7** disappeared, the color of solution changed from yellow to colorless. The reaction was quenched by adding MeOH and sat. $NaHCO_3$ solution. The organic layer was separated, dried over anhyd. Na_2SO_4, and condensed. Purification of the product was carried out by silica gel column chromatography using n-hexane-HOAc (2:1) as an eluent.

[General procedure for the preparation of 9]

To a CH_2Cl_2 solution (4 ml) of **7** (0.5 mmol, 120 mg), cooled at -78°C, was added a CH_2Cl_2 solution of $TiCl_4$ (1 M×0.5 ml), or a CH_2Cl_2 solution of $ZnCl_2$•OEt_2 (2.2 M×0.23 ml), and the resulting mixture was stirred for 5 min. A hexane solution of the organometallic reagent (0.55 mmol) was added, and the mixture was treated in a similar way as above. In the case of entry 5, the residue of Bu_3Sn part was removed as follows. The organic phase, after quenching the reaction, was vigorously stirred with 50% KF solution at room temperature, and then filtered through celite.

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