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DEVELOPMENT OF METHOD FOR EFFICIENT α-OXIDATION OF *tert*-ALKYLAMINES USING BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE

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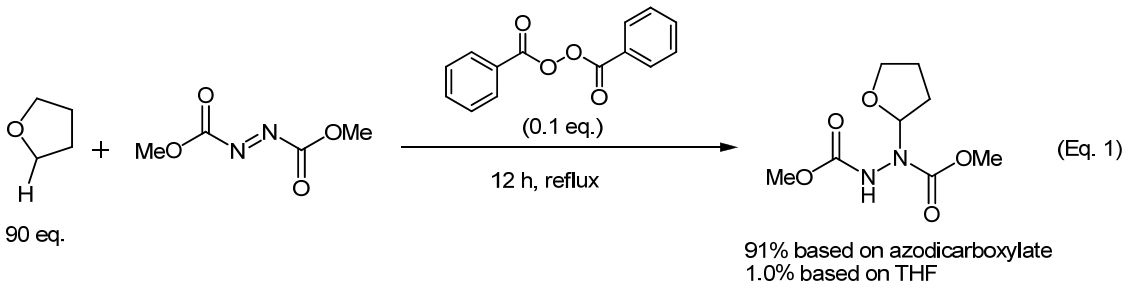
This paper is dedicated to Professor Dr. Victor Snieckus in celebration of his 77th birthday.

Abstract – An efficient α-oxidation of amines can be accomplished using bis(2,2,2-trichloroethyl) azodicarboxylate, which is more electrophilic than diethyl azodicarboxylate, often used in synthetic chemistry. *N*-Acetyl and *N*-*tert*-butoxycarbonylamines are good substrates for this α-oxidation, and in the case of *N*-phenylpyrrolidine an interesting dimerization reaction is followed by α-oxidation. The α-oxidation product can be transformed in the presence of nucleophiles and a Lewis acid to α-modified amines, presumably *via* an iminium intermediate.

The α-oxidation of heteroatom-containing compounds has enabled the development of interesting methodologies in organic synthesis. The well-known examples are sulfide α-oxidation (Pummerer reaction)[1] and amine α-oxidation (Polonovski reaction).[2] On the other hand, the α-oxidation of ethers has been reported to proceed *via* radical mechanism. A well-known example is the aerial autoxidation of ethers.[3]

We focus on the use of azodicarboxylates. Azodicarboxylates are widely used as Mitsunobu reagents in organic synthesis.[4] They are excellent electrophilic reagents used in hetero Diels-Alder,[5] hetero-ene,[6] Friedel-Crafts,[7] and other[8] reactions. Moreover, they react with ethers at the α-position, presumably *via* a radical mechanism (Eq. 1).[9]



However, the above reaction has a drawback, that is, ethers are mostly used as reaction solvents, so that the yield of adducts based on ether molecules is quite low. Despite this drawback, this reaction provides us with quite an interesting methodology. Therefore, we decided to examine this reaction using more reactive amine compounds as starting materials.[10]

First, we examined the effect of azodicarboxylates on the α-oxidation reaction (Table 1). We expected that changes in the electronic states of the ester group in azodicarboxylates will change the electrophilicity of the azo group. Therefore, we examined several azodicarboxylate derivatives for the reaction in search for optimal reaction conditions in the absence of a radical initiator. We chose *N*-acetylpyrrolidine, which has a similar structure to THF, as the substrate. The reaction with diethyl azodicarboxylate gave none of the desired product (Entry 1). Dipiperidine diamide, an efficient Mitsunobu reagent,[11] was used but the desired reaction did not proceed, and the substrate was recovered in good yield (Entry 2). In contrast, when a more electrophilic diphenyl azodicarboxylate[12] was used, we obtained the desired α-oxidation product in moderate yield (Entry 3); moreover, when bis(2,2,2-trichloroethyl) azodicarboxylate[13] was used,

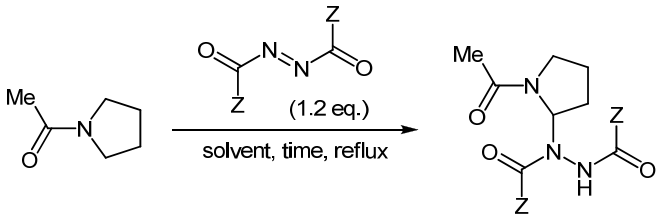


Table 1. Effects of azodicarboxylate and solvent in α-oxidation of amines

Entry	Z	Solvent	Boiling point (ºC)	Time (h)	Yield (%)	Recovery of substrate (%)
1	OCH_2CH_3	benzene	80	3	0	89
2	piperidinyl	benzene	80	3	0	81
3	OC_6H_5	benzene	80	3	43	37
4	OCH_2CCl_3	benzene	80	3	76 (93%)*1	18
5	OCH_2CCl_3	benzene	80	24	70	4
6	OCH_2CCl_3	toluene	110	3	68	7
7	OCH_2CCl_3	*p*-xylene	138	3	45	46
8	OCH_2CCl_3	chlorobenzene	132	3	78 (84%)*1	7

*1 Yields in parentheses were based on the recovery of *N*-acetylpyrrolidine.

we found that the α-oxidation product could be obtained in good yield (Entry 4). Increasing reaction time (3 to 24 h) led to a decreased yield, presumably because of the degradation of the α-oxidation product (Entry 5). From these results, bis(2,2,2-trichloroethyl) azodicarboxylate[14] was found to be a good α-oxidation reagent in the absence of a radical initiator. To further improve the yield, we examined the use of a solvent with a higher boiling point. The use of *p*-xylene led to a decrease in the yield, concomitant with an increased recovery of the substrate (Entry 7). The use of chlorobenzene gave a higher yield than that of *p*-xylene (Entry 8). Considering the substrate recovery, benzene was used for further studies.

To clarify the effect of the protecting group of amines on α-oxidation, several pyrrolidine derivatives were examined (Table 2). Unprotected pyrrolidine itself did not give an α-oxidation product, but an ester-to-amide exchange reaction occurred to give bisamide **A** (Entry 1).[13] *N*-Phenylpyrrolidine gave the dimerized products **B** and **B'**[15] (Entry 2). The dimerization mechanism seems to indicate that, from an α-oxidized amine, hydrazinedicarboxylate would be eliminated to give the iminium ion, part of which would isomerize to enamine. The [4+2] cycloaddition reaction between the iminium ion and enamine would give **B** and **B'**. High electron density on the nitrogen atom of *N*-phenylpyrrolidine might assist in the elimination of hydrazinedicarboxylate and promote the formation of the iminium ion. The reaction of *N*-*p*-toluenesulfonylpyrrolidine gave the desired product in low yield, and most of the starting material was recovered (Entry 3). The introduction of an amide group brought about a slight increase in the yield (Entry 4), and *N*-*tert*-butoxycarbonylpyrrolidine reacted similarly to *N*-acetylpyrrolidine (Entry 5). From these results, *N*-acetyl and *N*-*tert*-butoxycarbonyl groups seem to be suitable protecting groups for the α-oxidation of amines.

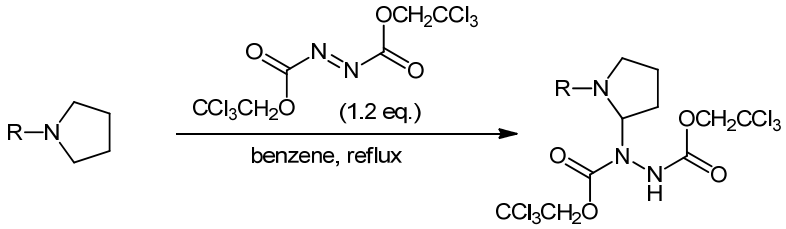
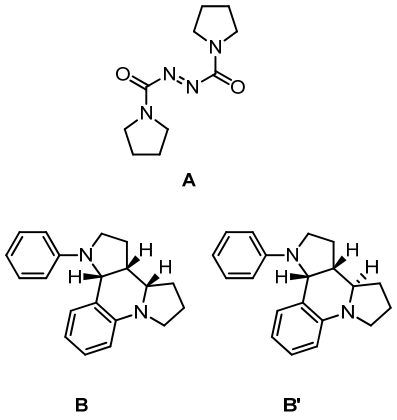


Table 2. Effects of protecting group in α-oxidation of amines

Entry	R	Time (min)	Yield (%)	Recovery of substrate (%)
1[*1]	H	4	-[*2]	-
2	C_6H_5	10	-[*3]	-
3	4-$MeC_6H_4SO_2$	180	23	67
4	C_6H_5CO	180	40	60
5	Me_3COCO	180	68	25

[*1] 2.0 eq. of pyrrolidine for azodicarboxylate was used for the reaction.
[*2] Bisamide **A** was produced in 76% yield.
[*3] **B** and **B'** were produced in 40% and 35% yields, respectively.



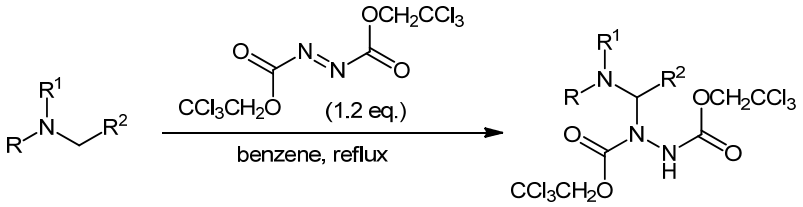
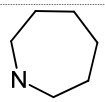
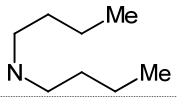
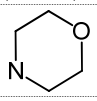
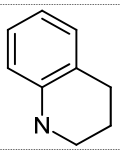
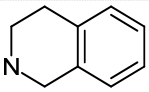


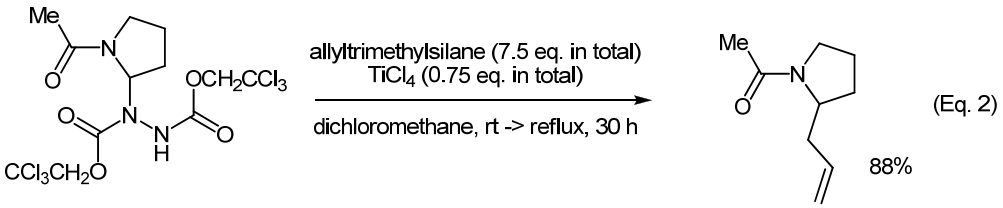
Table 3. Reactions of various amines with azodicarboxylate

Entry	R	R^1 R^2	Time (h)	Yield (%)	Recovery of substrate (%)
1	MeCO-		3	76	18
2	Me_3COCO-		3	68	25
3	MeCO-		12	42	51
4	Me_3COCO-		12	62	24
5	MeCO-		3	81	7
6	Me_3COCO-		3	93	-
7	Me_3COCO-		12	55	37
8	MeCO-		12	16	82
9	Me_3COCO-		12	12	85
10	MeCO-		12	24	45
11	Me_3COCO-		12	59	22
12	MeCO-		3	86	7
13	Me_3COCO-		3	96	-

We examined the scope of the amines, and the results are shown in Table 3. The reaction of cyclic amines gave unexpected results: the five- and seven-membered ring amines are reactive under the conditions used (Entries 1-2 and 5-6), but the six-membered ring amine seems unreactive (Entries 3-4). The acyclic amines reacted slowly (Entry 7). From these results, it was found that the substrates with moderate flexibility such as the 5- and 7-membered rings might be more appropriate for this reaction than those with rigid structures such as the 6-membered ring, or in contrast, than those with highly flexible alkyl chains. However, the reason for this remains unknown. *N*-Protected morpholine was examined. It was found that oxidation at the α-position of the nitrogen atom proceeded predominantly but in low yield (Entries 8-9). Tetrahydroquinoline derivatives gave α-oxidation products in low to moderate yields (Entries 10-11). Interestingly, oxidation occurred predominantly at the α-position of the nitrogen atom, not at the benzylic position. When tetrahydroisoquinoline derivatives were subjected to the reaction, oxidation occurred selectively at the methylene group between the nitrogen atom and unsaturated bonds (phenyl or alkenyl group) (Entries 12-13). These results suggest that the factors determining the selectivity of the reaction site

are complex. It seems likely that the α-position that possesses more acidic protons would be oxidized, but that other factors (e.g., steric circumstance, conformational tendency, and flexibility) might control the selectivity of the oxidation site.

gem-Diamino compounds, which could be produced by the α-oxidation of amines, could be regarded as a source of the acyliminium ion. This ion serves as a highly activated electrophile and might react with many nucleophiles to give α-modified amines. Indeed, we found that α-oxidation products could react with allyltrimethylsilane in the presence of titanium tetrachloride to give α-allylated *N*-acetylpyrrolidine in good yield (Eq. 2).



(Eq. 2)

In summary, we report a reaction that could introduce a hydrazinedicarboxylic ester group into the α-position of amines that could be regarded as an iminium ion equivalent, often utilized as a reactive species in synthetic chemistry. The scope and limitation of the reaction are not yet fully elucidated[16], but we could estimate the reaction outcome when cyclic amines are used as substrates. Further studies will be conducted in due course to elucidate the generality of the reaction.

Typical General Procedure: Reaction of *N*-acetylpyrrolidine. *N*-Acetylpyrrolidine (113 mg, 1.00 mmol) was dissolved in benzene (3.3 mL), and bis(2,2,2-trichloroethyl) azodicarboxylate (457 mg, 1.20 mmol) was added to the resulting solution. After stirring the mixture under reflux for 3 h, it was cooled to room temperature, and the solvent was removed under reduced pressure. Purification by column chromatography [eluent: *n*-hexane-EtOAc (2 : 1)] gave the product (374 mg, 76%) as a colorless foam. ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.80-2.00 (br s, 1H), 2.05-2.16 (m, 3H), 2.08-2.65 (m, 3H), 3.40-3.94 (m, 2H), 4.38-5.23 (m, 4H), 5.82-6.22 (m, 1H), 6.50-6.70 (br s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 21.9, 22.1, 22.2, 22.9, 28.5, 33.5, 46.8, 48.2, 70.5, 73.0, 74.9, 75.3, 75.7, 94.8, 95.0, 153.1, 155.1, 170.8, 171.5 (possible mixture of rotamers corresponding to carbamoyl groups).

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15. The structures of **B** and **B'** were determined by measuring 2D NMR (DQF-COSY, HMQC, HMBC and NOESY), as well as by high-resolution mass spectrometry.
16. The mechanism of the reaction could not be elucidated, but the use of radical scavengers such as galvinoxyl, iodine and edaravone, showed no marked inhibition of this reaction. From the results, it seems likely that the α-oxidation of amines by azodicarboxylate proceeds mainly in an ionic mechanism.