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Regio and Diastereoselective Addition of Imidazoline 3-oxides to Aryl Isocyanates

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Abstract: Δ^3-Imidazoline 3-oxides ***1*** underwent regio and diastereoselective cycloaddition with aryl isocyanates ***2*** to give 5,6,7,7a-tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1H)-ones ***3*** in excellent yields. Thermally and chemically induced retro cycloaddition of compounds ***3*** was demonstrated.
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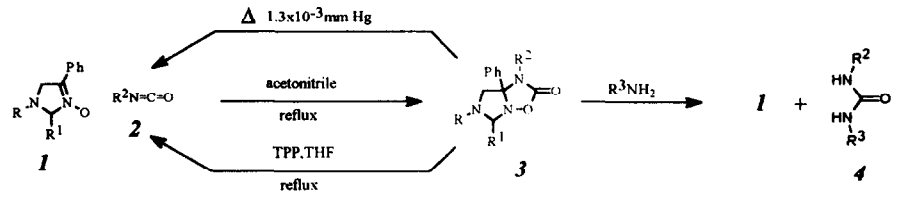
1,3-Dipolar cycloaddition reactions are excellent for the synthesis of five-membered heterocyclic rings. The commonly used 1,3-dipoles are diazoalkanes, alkyl and allyl azides, nitrile imines, nitrile ylids and nitrones.[1]

The 1,3-dipolar cycloaddition reaction of nitrones with olefins, acetylenes, isocyanates, isothiocyanates and thiocarbonyl compounds has been reported.[2-4] The 1,3-dipolar cycloaddition reaction of pyridine 1-oxide with phenyl isocyanate gave 2-anilinopyridine. The C-acylnitrone type of quinoxalin-2-one 4-oxides have also been reported to react with aryl isocyanates to give 3-arylaminoquinoxalin-2-ones via an oxadiazolone intermediates.[5]

To our knowledge no examples of cycloaddition of imidazoline N-oxides with isocyanates have been reported.

We herein report the synthesis of a new class of 5,6,7,7a-tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1H)-ones by cycloaddition of Δ^3-imidazoline 3-oxides with aryl isocyanates and thermally or chemically induced retro cycloaddition reaction of compounds ***3***.[6]

Cyclic nitrones ***1***, readily prepared by methods which we have already reported,[7-9] reacted with aryl isocyanates in refluxing acetonitrile or THF to give the corresponding imidazooxadiazolones ***3*** as the sole regioisomer in excellent yields. The cycloaddition of nitrones ***1f-j*** to aryl isocyanates gave exclusively one diastereomer. The steric hindrance of the aryl group at C-2 on the nitrone seems to be responsible for the approach of the 2π fragment from the opposite side. The energy minimized conformations of the cis- and trans-diastereomers showed that cis should be thermodynamically more stable than the trans. We assume that the approach of the 2π fragment from the side opposite to the aryl group at C-2 involves lower-energy transition state and leads to the formation of cis-imidazooxadiazolone ***3***.



Scheme 1

Table1. Imidazooxadiazol-2-ones

entry	yield of *3*(%)	R	R^1	R^2	mp (°C) (solvent)	IR(KBr) $cm^{-1}\nu_{C=O}$
a	100	4-$CH_3C_6H_4$	H	Ph	159-160[a]	1745
b	100	4-$MeOC_6H_4$	H	Ph	161.5[a]	1745
c	98	4-$CH_3C_6H_4$	H	4-$MeOC_6H_4$	80-81[b]	1750
d	95	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	114-115[b]	1750
e	97	4-$CH_3C_6H_4$	H	2-$MeOC_6H_4$	133-135[b]	1756
f	90	Ph	2,3$(MeO)_2C_6H_3$	Ph	159-160[c]	1775
g	93	Ph	2,3$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	157-158[c]	1775
h	90	Ph	2,3$(MeO)_2C_6H_3$	2-$MeOC_6H_4$	169-170[c]	1770
i	92	4-$MeOC_6H_4$	Ph	Ph	143-144[a]	1775
j	95	4-$MeOC_6H_4$	Ph	4-$MeOC_6H_4$	153-155[b]	1775

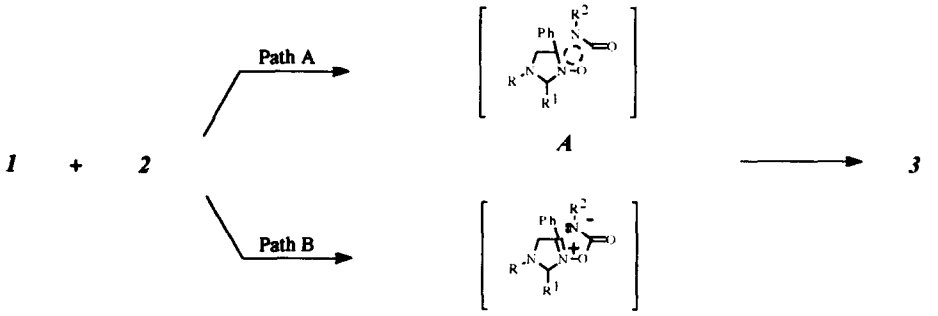
[a] = acetonitrile; [b] = ether-petroleum ether; [c] = ethanol

Two distinct mechanistic pathways may account for the formation of imidazooxadiazolones *3*. Path A (Scheme 2) involves (4+2) cycloaddition of imidazoline N-oxide *1* with aryl isocyanate *2*. In this process, isocyanate *2* should react as a dipolarophile. A nucleophilic attack by imidazoline N-oxide *1* on the electrophilic carbon of the aryl isocyanate *2* should lead to intermediate ***B*** (Path B; Scheme 2) which undergoes cyclization to give *3*.

The structures of *3* were established on the basis of their IR, ^1H NMR and MS spectra. Carbonyl absorptions of compounds ***3a-j*** are given in table 1. In the proton magnetic resonance spectra of ***3a-e***, AB systems centered approximately at δ 3.85 (J_{AB} = 10.85 Hz) and δ 4.72 (J_{AB} = 10.24 Hz) both equivalent to two protons have been assigned to protons at C-5 and C-7 respectively. In the mass spectra of ***3a-e*** the molecular ion peaks are absent. This is expected as the cycloadducts are thermolabile. Thus in its mass spectra, these

cycloadducts underwent a retro cycloaddition as is indicated by the parent ion peaks which correspond to 1,4-diarylimidazoles formed by loss of water from the *1a-e*.

In the ^{1}H NMR spectra of *3f-j* an AB system approximately at δ 4.30 is due to the protons at C-5 and a singlet at δ 6.00-6.50 equivalent to one proton is assigned to proton at C-7. In the mass spectra of these compounds parent ion peaks correspond to the product of retro cyclization and in some cases to the product of retro cyclization and dehydration. NOE experiments performed for *3g* permitted a tentative assignment of the configuration of compounds *3f-j*. Irradiation of proton at C-7 led to signal enhancement for methoxy groups' protons at N-3 and C-7 aryl groups (38%, 22.7% and 31.81% respectively). Thus, the NOE results are supporting a configuration with cis oriented C-7 proton and N-3 aryl. Assuming that N-3 aryl group should be trans to the phenyl at C-4 we concluded that later and those at C-7 should be cis to each other.



Scheme 2

In order to induce a retro 1,3-dipolar cycloaddition reaction, compound *3i* was refluxed in THF for 24 hr but no reaction was observed. However when *3i* was treated with a four fold excess of triphenylphosphine (TPP) in refluxing THF the products of the reaction were nitrone *1i* and aryl isocyanate. When we attempted to react compound *3i* and L-tryptophan methyl ester in refluxing THF the products isolated were again nitrone *1i* and the disubstituted urea which was synthesized separately from aryl isocyanate and tryptophan methyl ester. We repeated the reaction with aniline and the result was analogous of with tryptophan methyl ester. After 50 hr heating compound *3i* with four fold excess of the amine the reverse reaction gave almost quantitatively the nitrone *1i* and corresponding diphenylurea.

Furthermore we have achieved retro-cycloaddition reactions by heating *3* in the condensed phase under vacuum (see table 2). Thermal treatment of compounds *3a-e* led exclusively to the formation of compounds *1*. In the case of *3f* aryl isocyanate was eliminated but the formed N-oxide undergo dehydration to give the corresponding imidazole. In case of *3i* where the aryl group at C-2 is unsubstituted the resulting product was nitrone *1i*.

Table 2. Retro Cycloaddition of Compounds ***3***.

Starting material	React. temp.[a]	React. time[b]	product[d]	yield (%)	Starting material	React. temp.	React. time	product	yield (%)
3a	165	20	***1a***	97	***3e***	160	15	***1a***	96
3b	165	20	***1b***	98	***3f***	160	5	***1f***[c]	0
3c	160	15	***1a***	98	***3i***	155	15	***1i***	90
3d	160	15	***1b***	95					

[a] Reaction temperatures are in °C [b]; Reaction time in min.; [c]The product of dehydration of the corresponding imidazoline N-oxide. [d]Compounds 3a-f,i were thermolysed at 1.3×10^{-3} mmHg.

REFERENCES AND NOTES

1. Norman, R.O.C. *Principles of Organic Synthesis*; Chapman and Hall: London, ***1978***; pp.296-299.
2. Padwa, A.; *Angew. Chem.* ***1976***, 88, 131-144 and references cited therein.
3. Oppolzer, W. *Angew. Chem.* ***1977***, 89, 10-24.
4. Beckmann, E. *Ber.*, ***1890***, 23, 3331-3341, ibid. 1894, 27, 1957-1959.
5. Kurasawa, Y.; Takada, A.; Kim, H.S. *J. Heterocyclic Chem.* ***1995***, 32, 1085-1114.
6. To the best of our knowledge these are first examples of 1,3-dipolar cycloaddition of imidazoline N-oxides to isocyanates and retro 1,3-dipolar cycloaddition of imidazooxadiazolones.
7. Coşkun, N.; Sümengen, D. *Synth. Commun.* ***1993***, 23, 1699-1706.
8. Coşkun, N.; Asutay, O.; Sümengen, D. *Chim. Acta. Turc.* ***1996***, 24, 165-167.
9. Coşkun, N.; Asutay, O. *Chim. Acta. Turc.* in press.

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