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Secondary Amine Mediated Ring-Opening of Tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-ones

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5,6,7,7a-Tetrahydroimidazo [1,5-*b*][1,2,4]oxadiazol-2(1*H*)-ones **1a-g** converted to imidazoles in the presence of secondary amines. *cis*-Imidazooxadiazolones **1d-g** gave the imidazoles **4d-g** when treated with secondary amines, while the treatment of these compounds with tertiary amines afforded imidazoline 3-oxides **5d-g**. In case of **1a-c**, where R^1 is a hydrogen, tertiary amines induced elimination to give imidazoles **4a-c**. In the case of **1a-c**, probable *trans* elimination caused by triethylamine and pyridine and in the case of **1d-f**, a concerted double *cis* elimination mediated by secondary amines is discussed.

Introduction

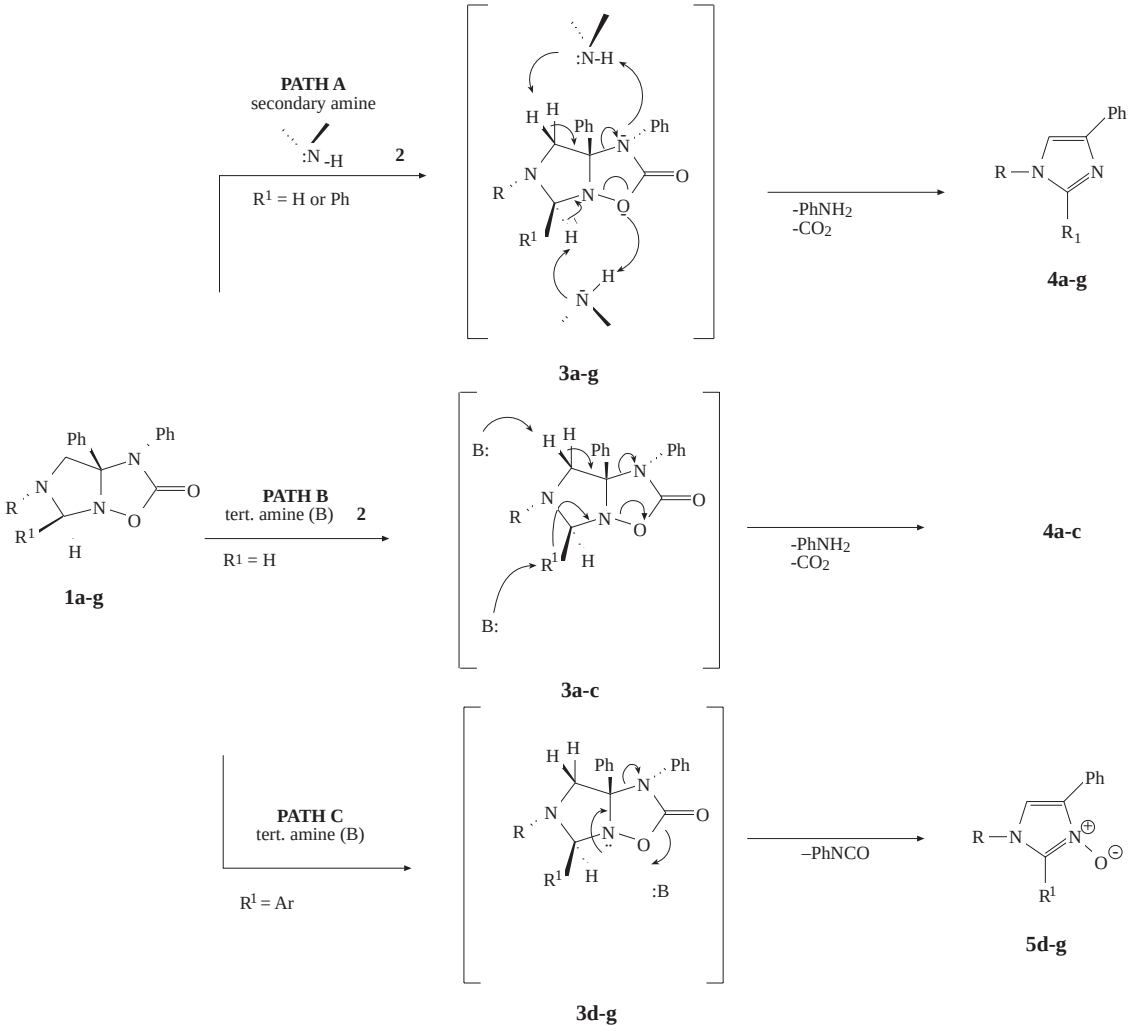
Recently we reported the regio- and diastereoselective synthesis of 5,6,7,7a-tetrahydroimidazo [1,5-*b*][1,2,4] oxadiazol-2(1*H*)-ones by the reaction of Δ^3-imidazoline 3-oxides with aryl isocyanates[1]. The *cis* assignment for the compounds possessing two chiral carbon atoms was made on the basis of NOE experiments. The reactions of compounds **1** with TPP and primary amines were also investigated. The synthesis and X-ray analysis of the adducts obtained from imidazoline 3-oxides and DMAD was also reported by us[2]. As a continuation of our interest in this field, we examined the reactions of adducts **1** with secondary and tertiary amines.

We herein report the conversion of 5,6,7,7a-tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-ones **1a-g** to imidazoles induced by secondary amines, and retro 1,3-dipolar cycloaddition of compounds **1d-g** induced by tertiary amines.

Results and Discussion

Imidazooxadiazolones **1a-g** reacted with secondary amines such as diethylamine (**DEA**) and piperidine (**PPN**) to give imidazoles **4a-g** in high yields. If the reaction of secondary amines with imidazooxadiazolones is analogous with that of primary amines[1], we should detect corresponding imidazoline 3-oxide and urea. However, neither 3-oxide nor urea were detected in the reaction mixture. Instead, aniline was detected in the reaction mixtures, which should be the product of decarboxylation of the phenylcarbamic acid. It was obvious that secondary amines act as bases rather than nucleophiles in this reaction. In the cases of **1a-c** the ring-opening may involve two synchronous E_2 reactions because there are hydrogen atoms at the imidazole

ring obeying the stereochemical requirement[3] to be trans to the leaving groups' atoms. The ring-opening of **1a-c** (Scheme, $R^1 = H$ path B) in the presence of tertiary amines such as TEA and pyridine should proceed in E_2-like manner (see Scheme). As a result, compounds **1a-c** convert to imidazoles in the presence of both types of amines, although the reaction of **1a-c** with tertiary amine is slower than the reaction with secondary amines (see Table). However, significantly different behaviour of *cis* diastereomers **1d-g** was observed when reacted with secondary and tertiary amines. Secondary amines, especially PPN, easily convert **1d-g** to the corresponding imidazole, while under similar conditions the same compounds remain unchanged or give, retro 1,3-dipolar cycloaddition reaction when treated with tertiary amines. For example, compounds **1d-g** convert to imidazoles when refluxed in THF in the presence of PPN for 2.5 h, but they remain unchanged when TEA or pyridine are used as amines in spite of 6 h reflux in the same solvent. Prolonged reaction time ensured the conversion of **1d-f** to imidazoline 3-oxides but not to the imidazoles.



Scheme

The treatment of compounds **1d-f** with TEA or pyridine in acetonitrile at reflux for 18 h led to the formation of corresponding imidazoline 3-oxides in high yields (see Table). The reaction of **1f** with PPN was repeated in acetonitrile and the product formed was again imidazole **4f** (see Table). In regard to these findings, we assume that TEA and pyridine probably convert compounds **1a-c** in a manner identical to those

in the E_2 reactions. The fact that they did not convert **1d-f** to imidazoles confirms our *cis* assignment for compounds **1d-g**. The ability of the secondary amines to form hydrogen bonds is probably the reason for their easy coordination to the imidazooxadiazolone ring system. The elimination processes in these cases may involve synchronous hydrogen bonding and abstraction of the protons at C-2 and C-4 of the imidazole ring via a transition state shown in the scheme (path A). If we assume that the transition state is as illustrated in the scheme (path A), there we can not ignore the fact that the final product is an aromatic imidazole and this probably is one of the driving forces of the ring-opening discussed.

Table. Reaction of imidazooxadiazolones **1a-g** with secondary and tertiary amines.

Start. material	**R**	**R**[1]	Amine	RT	Product	Yield (%)
1a	Ph	H	**DEA**	18a	**4a**	85
			PPN	2.5[a]	**4a**	87
			TEA	24[b]	**4a**	70
1b	p-MeC_6H_4	H	**DEA**	18[a]	**4b**	80
			PPN	2.5[a]	**4b**	95
			TEA	24[b]	**4b**	60
			Py	24[b]	**4b**	65
1c	p-$MeOC_6H_4$	H	**DEA**	18[a]	**4c**	90
			PPN	2.5[a]	**4c**	96
			TEA	24[b]	**4c**	65
1d	p-MeC_6H_4	4-$MeOC_6H_4$	**DEA**	18a	**4d**	78
			PPN	2[a]	**4d**	83
			TEA	18c	**5d**	75
1e	p-$MeOC_6H_4$	Ph	**DEA**	24[a]	**4e**	60
			PPN	2.5[a]	**4e**	97
			TEA	6[b]	**4e**	0
				18c	5e	91
1f	p-MeC_6H_4	Ph	**DEA**	18[a]	**4f**	80
			PPN	2.5[a]	**4f**	98
				2c	**4f**	90
			TEA	6[b]	**4f**	0
				18c	5f	90
			Py	6[b]	**4f**	0
				18c	5f	70
1g	p-MeC_6H_4	3,4(OCH_2O)C_6H_4	**DEA**	18[a]	4g	82
			PPN	2.5[a]	4g	92

DEA = Diethylamine; **PPN** = Piperidine; **TEA** = Triethylamine; **Py** = Pyridine. RT = reaction time in hours; [a] = the amine used as a solvent; [b] = THF; [c] = acetonitrile.

The significant reaction rate difference in the case of DEA and PPN prompted us to think that TEA, the bulkiest of the amines used in this investigation, could not promote the ring-opening of **1d-f** due to sterical reasons. If this were the reason, the reactivity of pyridine would be similar to that of PPN, but experimental results did not confirm this assumption.

The value of this ring-opening lies not only in the possibility for easy conversion of imidazoline 3-oxides to imidazoles via imidazooxadiazolones but also in its stereospecificity. The fact that secondary amines easily convert cis imidazooxadiazolones to imidazoles but not tertiary amines means they may serve as a useful

diastereoconfiguration assignment test[2] for compounds of this type and probably for other bicyclic systems involving tetrahydroimidazo ring annelated to other rings via heteroatoms such as oxygen, nitrogen and sulphur.

The imidazoles[4] obtained by the ring-opening of imidazooxadiazolones **1** were proved to be identical with those prepared from the corresponding imidazoline 3-oxides[5,6] by the method which we have already reported[7].

Experimental

Melting points were taken on a Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. Proton magnetic resonace spectra were recorded on a Varian 200 MHz spectrometer. Mass spectra were routinely recorded at 70 eV by electron impact on a Hewlett Packard GC-MS. Analytical thin layer chromatography (TLC) was done on Kiselgel 60 F_{254} (E. Merck). Visualization was effected with UV light. Freshly prepared imidazooxadiazolones were used after recrystallization from either ethanol or acetonitrile.

Preparation of imidazooxadiazolones 1. Starting imidazooxadiazolones **1a-g** were prepared according to the procedure[1] described by us. Compounds **1b, c, e, f** were characterized in our previous work. **1a, d, g** are newly prepared compounds and were characterized by their IR and ^{1}H NMR spectra.

1a. The compound was obtained in 90% yield and recrystallized from ethanol. Mp 143°C. IR (KBr) $\nu_{C=O}$ 1750 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.60 (1H, d, J = 10.8), 4.20 (1H, d, J = 10.8), 4.50 (1H, d, J = 10.2), 5.0 (1H, d, J = 10.2), 6.65 (5H, m), 7.20-7.45 (10H, m). Anal. Calcd for $C_{22}H_{19}N_3O_2$ (357.42): C, 73.93; H, 5.36; N, 11.76. Found C, 73.87; H, 5.40; N, 11.75

1d. Yield 84%. Mp 137-138°C (recrystallized from ethanol). IR $\nu_{C=O}$ 1775 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ2.24 (3H, s), 3.70 (3H,s), 4.30 (2H, s), 5.90 (^{1}H, s), 6.60 (2H, d, J = 9.0), 6.80 (2H, d, J = 9.0), 6.90-7.20 (6H, m), 7.30-7.45 (8H, m). Anal. Calcd for $C_{30}H_{27}N_3O_3$ (477.57): C, 75.45; H, 5.70; N, 8.80. Found C, 75.40; H, 5.68; N, 8.75

1g. Yield 90%. Mp 142-142.5°C (recrystallized from ether). IR $\nu_{C=O}$ 1775 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ2.24 (3H, s), 4.31 (2H, s), 5.80 (2H, s), 5.90 (^{1}H, s), 6.53 (2H, d, J = 9.0), 6.72 (2H, d, J = 9.0), 6.90-7.10 (5H, m), 7.20-7.40 (8H, m). Anal. Calcd for $C_{30}H_{25}N_3O_4$ (491.55): C, 73.31; H, 5.13; N, 8.55. Found C, 73.25; H, 5.15; N, 8.50

Reaction of compounds (1) with secondary amines. General Procedure - Imidazooxadiazolone **1** (0.202 mmol) was dissolved in diethylamine or piperidine (10 mL) and the mixture was refluxed (See Table for the reaction times). The reaction was stopped and the solvent was evaporated. The residue was extracted with warm hexane (3 × 10 mL). The combined extracts were concentrated and left to cool. The formed crystals were collected by filtration. The imidazole was identical to that obtained by dehydration of the corresponding imidazoline 3-oxide.

*Reaction of **1a** with diethylamine:* Imidazooxadiazolone **1a** (0.0721 g, 0.202 mmol) was dissolved in diethylamine (10 mL) and the mixture refluxed for 18 h. The reaction was stopped and the solvent was evaporated. The residue was subjected on a silica gel coated plate and developed with a solvent mixture (chloroform:hexane:methanol:acetone, 4.5:4:1:0.5). The band containing the imidazole was eluted with chloroform. Yield 85%. The compound was identical to those obtained by dehydration of the corresponding

imidazoline 3-oxide.

*Reaction of **1a** with piperidine:* Compound **1a** (0.0721 g, 0.202 mmol) was dissolved in 10 mL of piperidine and refluxed for 2.5 h. The solvent was evaporated and the product isolated by preparative TLC. Yield 87%.

Reaction of **1b** with diethylamine: Imidazooxadiazolone **1b** (0.075 g, 0.202 mmol) was dissolved in diethylamine (10 mL) and the mixture refluxed for 18 h. The reaction was stopped and the solvent was evaporated. The residue was extracted with warm hexane (3 x 10 mL). The combined extracts were concentrated and left to cool. The formed crystals were collected by filtration. The compound was identical to those obtained by dehydration of the corresponding imidazoline 3-oxide.

*Reaction of **1b** with piperidine:* Compound **1b** (0.075 g, 0.202 mmol) was dissolved in 10 mL of piperidine and heated at 56°C for 2.5 h. The solvent was evaporated and the product (**4b**) isolated by preparative TLC.

*Reaction of **1f** with piperidine:* A solution of compound **1f** (0.050 g, 0.1 mmol) in piperidine (3 ml) was heated at 60°C for 2.5 h. The solvent was evaporated under reduced pressure and the residue was extracted with warm hexane (4 × 1 mL). The combined extracts were concentrated and left to cool at room temperature. The formed yellowish plates were collected by filtration to give 30 mg (yield 98%) of pure 1-p-tolyl-2,4-diphenylimidazole. The compound was identical in all respects with the authentic sample. Mp 144.5-145°C [7,10].

*Reaction of **1f** with diethylamine:* A solution of **1f** in 5 mL of diethylamine was refluxed for 18 h. The work up procedure is as in the previous reaction. The corresponding imidazole was obtained in 80% yield and was compared with the authentic sample.

Reaction of compounds (1a-c) with tertiary amines. General Procedure - To a solution of **1**(0.2 mmol) in 5 mL of THF, amine (1.5 mL) was added and the mixture was stirred at reflux for 24 h. The solvent and the base were removed under reduced pressure and the residue was extracted with warm hexane (4 × 3 mL). The solvent was reduced to 5 mL and left to crystallize at room temperature. The product was characterized to be the corresponding imidazole.

*Reaction of **1b** with triethylamine:* To a solution of **1b** (0.050 g, 0.13 mmol) in 5mL of THF, triethylamine (1.5 mL) was added and the reaction mixture was stirred at reflux for 24 h. The solvent and the catalyst were removed under reduced pressure and the residue was extracted with warm hexane (4 × 3 mL). The solvent was reduced to 5 mL and left to crystallize at room temperature. The product was characterized to be the corresponding imidazole.

Reaction of compounds (1d-f) with tertiary amines. General Procedure - To a solution of compound **1**(0.2 mmol) in 5 mL of acetonitrile, amine (1 mL) was added and the reaction mixture was refluxed for 18 h. The solvent and the excess of the amine were evaporated under reduced pressure and the residue was heated and dissolved in heating and left to crystallize[8] The compounds were collected by filtration and proved to be imidazoline 3-oxides by comparing with authentic samples[5,6].

*Reaction of **1e** with triethylamine:* To a solution of compound **1e** (0.025 g, 0.05 mmol) in 3 mL of THF, triethylamine was added (1 mL) and the reaction mixture refluxed for 6 h. TLC controls showed that no conversion occurs. The solvent and triethylamine were removed under reduced pressure and the residue was heated and dissolved in acetonitrile and left to crystallize. The compound (starting **1e**, by comparing mps and ir spectra) was recovered in 95% yield.

Acknowledgement

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4. **4a.** Mp 93-94.2°C (recrystallized from ether-hexane, 1:2); *m/z* 220 (M^+); ^{1}H NMR δ ppm ($CDCl_3$) 7.32 (1H, s, CH-5), 7.40-7.50 (5H, m, Ar-H), 7.62 (1H, s, CH-1). 7.80-7.90 (5H, m, Ar-H); Anal. Calcd for $C_{15}H_{12}N_2$ (220.28)C, 81.79; H, 5.49; N, 12.72. Found 81.80; H, 5.49; N, 12.71 **4b**. Mp 134-135°C (recrystallized from ether); *m/z* 234 (M^+); ^{1}H NMR δ ppm ($CDCl_3$) 2.41 (3H, s, MeO), 7.25-7.40 (7H, m, Ar-H), 7.53 (1H, s, CH-5), 7.82 (1H, s, CH-2), 7.85 (2H, m, Ar-H); Anal. Calcd for $C_{16}H_{14}N_2$ (234.30) C, 82.02; H, 6.02; N, 11.96. Found C, 82.00; H, 6.12; N, 11.90 **4c**. Mp 100-101 (recrystallized from ether-hexane, 1:2), *m/z* 250 (M^+); ^{1}H NMR δ ppm ($CDCl_3$) 3.85 (3H, s, Me), 7.00 (2H, d, J = 8.0, Ar-H), 7.25-7.40 (5H, m, Ar-H), 7.49 (1H, s, CH-5), 7.82 (3H, m, CH-2, Ar-H); Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30) C, 76.78; H, 5.64; N, 11.19. Found C, 76.70; H, 5.65; N, 11.20 **4d**. oil, *m/z* 340 (M^+); ^{1}H NMR δ ppm ($CDCl_3$) 2.35 (3H, s, Me), 3.74 (3H, s, MeO), 6.90 (2H, d, J = 8.0, Ar-H), 7.20-7.45 (10H, m, Ar-H), 7.95 (2H, m, ArH); Anal. Calcd for $C_{23}H_{20}N_2O$ (340.43) C, 81.15; H, 5.92; N, 8.23. Found C, 81.12; H, 5.87; N, 8.20 **4e**. Mp 110°C, lit[7,9] mp 110°C; **4f**. Mp 144.5-145°C, lit[7,10] mp 148°C; **4g**. Mp 109-109.7 (recrystallized from ether), *m/z* 354 (M^+); ^{1}H NMR δ ppm ($CDCl_3$) 2.25 (3H, s, Me), 5.98 (2H, s, OCH_2O), 6.80-7.45 (1^1H, m, ArH), 7.95 (2H, d, J = 8.0, ArH); Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.41) C, 77.95; H, 5.12; N, 7.90. Found C, 77.90; H, 5.12; N, 7.91
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8. In the case of **1d**, after heating for 18 h the corresponding imidazoline 3-oxide precipitated in the reaction mixture. The compound was filtered and to the filtrate aniline was added and the mixture heated in a water bath for 15 min. The solvent was evaporated and the residue was dissolved in 1mL of ethanol and left to crystallize. The product isolated was shown to be diphenyl urea by comparing with authentic samples.
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