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A General, One-Pot Method for the Synthesis of 2-Substituted Oxazoles

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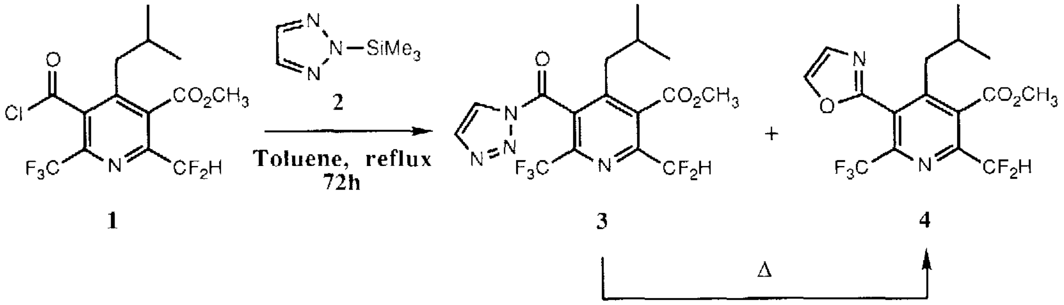
Abstract: *The reaction of 2-trimethylsilyl-1,2,3-triazole with acid chlorides readily forms triazole amides. The triazole amides, when heated to 150°C in sulfolane, rearrange with the elimination of nitrogen to give 2-substituted oxazoles in high yields. The oxazole synthesis is general, and can be carried out in one-pot.*

Oxazoles have been of interest due to their utility as Diels-Alder dienes in the synthesis of furans[1] and pyridines.[2] They have also been used as protecting groups[3], and are found in natural products.[4] A variety of syntheses of 4- and 5-substituted oxazoles exist,[5] but few methods are available if one desires the 4- and 5-positions unsubstituted. Commonly, oxidations of oxazolines with nickel peroxide are used when 2-substituted oxazoles are desired.[6] This method is troublesome and not generally high yielding.

Herein we report a simple high yielding synthesis of 2-substituted oxazoles from acid chlorides and 2-trimethylsilyl-1,2,3-triazole.[7] Upon reacting the hindered pyridine acid chloride **1** with 2-trimethylsilyl-1,2,3-triazole **2** in refluxing toluene for three days, we isolated the expected triazole amide **3** in a 25% yield along with the pyridyl oxazole **4** in a 45% yield. By heating **3** alone we were able to confirm that **4** was being formed by a nitrogen elimination rearrangement reaction of the triazole amide **3**. We found only one literature example of this reaction, and this report did not disclose any synthetic utility.[8]



As shown by entries 1 and 2 in Table I, the conversion of the triazole amides to the oxazoles is quite sluggish in either refluxing toluene or xylenes. We have also found that the reaction is not effected photochemically.[9,10] It is believed the reaction proceeds by heterolysis of the N1-N2 bond of the triazole amide to give a zwiterionic intermediate **5**. This intermediate can then rapidly undergo an intramolecular displacement of nitrogen to give the oxazole.

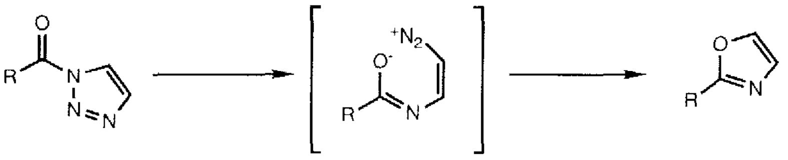


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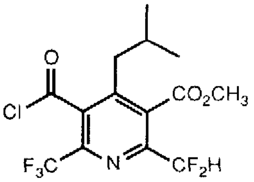
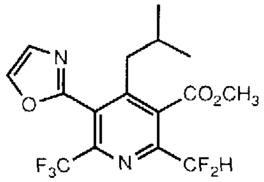
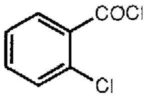
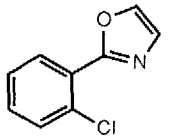
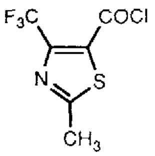
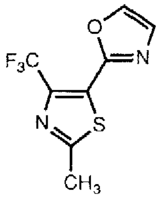
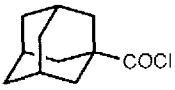
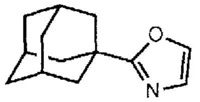
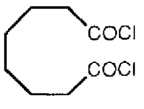
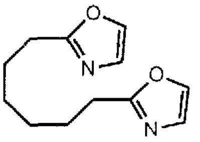
Table I: Conversion of Acid Chlorides to Oxazoles

Entry	Substrate	Product[a]	Method	% Yield[b]
1			A	45[c]
2			B	82
3	[Entry 2]	[Entry 2]	C	91
4			D	86
5			D	73
6			D	37[d]

[a]All new compounds gave ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis consistent with the structure shown; [b]Yield data is for isolated homogeneous material; [c]Reaction was stopped before total conversion of amide to oxazole; [d]Isolated yield is low due to isolation difficulties. Actual conversion is much higher than the yield indicates.

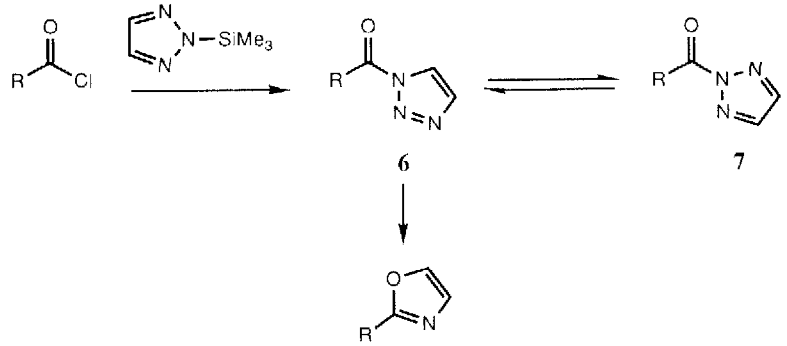
Methods A: Refluxing toluene 3 days; **B**: Refluxing xylenes 7 days; **C**: Sulfolane 140°C 3 hours; **D**: Sulfolane 150°C 2 hours.

If ionic intermediates were involved we reasoned that the use of polar solvents should increase the rate of the reaction. Reactions in DMF were not satisfactory because of the formation of dimethylamides. The use of sulfolane as a solvent greatly increased the rate of the reaction, and did not promote the formation of side products. Comparing entries 2 and 3 in Table I, one can see a greater than 50X rate enhancement at 140°C in sulfolane verses xylenes.

Typical Procedure (Entry 4): To a solution of 5-chlorocarbonyl-2-methyl-4-trifluoromethylthiazole (4.6 g, 20 mmol) in 20 mL of sulfolane was added 2-trimethylsilyl-1,2,3-triazole (3.4 mL, 22 mmol) in one portion. A slight exotherm takes the reaction to 35°C. The reaction mixture was placed under vacuum (~65 torr), while being heated to 40 - 45°C for five minutes, to remove the chlorotrimethylsilane byproduct. The reaction mixture was then heated under nitrogen at 150°C for 2.5 hours. The reaction was poured into 120 mL of water followed by extraction with ether. The ether extracts were washed with water then brine, and dried over anhydrous sodium sulfate. Concentration gave the crude product which was passed through a plug of silica gel (eluted with ethyl acetate:hexanes = 1:5) to remove traces of sulfolane and polar impurities. Isolated 4.01 g (86% yield) of the oxazole (MP 93.5 - 95°C, recrystallized from hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, oxazole C-5 H), 7.22 (s, oxazole C-4 H), 2.71 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 167.70 (s, oxazole C-2), 153.03 (s, 1C), 141.06 (q, 1C, $J_{C\text{-}F}$ = 37.6 Hz), 140.22 (s, oxazole C-5), 129.09 (s, oxazole C-4), 126.08 (s, 1C), 120.12 (q, 1C, $J_{C\text{-}F}$ = 272 Hz), 19.12 (s, 1C).

The only difficulty that the reaction presented was the isolation of highly polar and/or volatile products from the sulfolane solvent (table I entry 6). *In such cases, reverse phase chromatography may be necessary for* purification.

In following the progression of the triazole amide to oxazole conversion, one can observe the formation and equilibration of two triazole amide isomers. Initially, the N1-triazole amide **6** forms from the reaction of the silyltriazole with the acid chloride. Upon heating an equilibrium mixture forms of the N1- **6** and N2-triazole amides **7**. The two isomeric amides remain in equilibrium through the reaction. An equilibrium is evident because the relative concentrations of the two isomers remains the same over the course of the reaction, and one would presume that the oxazole is formed only from the N1-triazole amide **6**. This equilibrium has been reported in literature for N-acetyl-1,2,3-triazole.[11]



In terms of ease and efficiency, we feel the synthesis of 2-substituted oxazoles by the described procedure represents a significant improvement over previously described methods. In order to expand the scope of this method, we would like to look at extensions of this reaction for the synthesis of thiazoles from thioacid chlorides, and imidazoles from iminoyl chlorides. Additionally, it would be useful to explore the regiochemical outcome of using substituted silyltriazoles.

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7. 2-Trimethylsilyl-1,2,3-triazole was purchased from Aldrich Chemical Co., and is also available from Pfaltz & Bauer. For the preparation of 2-trimethylsilyl-1,2,3-triazole see: Birkofer, L.; Wegner, P. *Chem. Ber.* **1966**, 99, 2512-2517.
8. In the following paper, reference was made to the thermolysis of 1-benzoyl-4,5-diphenyl-1,2,3-triazole at 254°C in biphenyl to give a 29% yield of 2,4,5-triphenyloxazole: Huisgen, R. *Angew. Chem.* **1960**, 72, 359-390.
9. Irradiation of a sample of 1-(2-chlorobenzoyl)-1,2,3-triazole (Table I, entry 2) in acetonitrile, through quartz, with a 450W Hanovia lamp, resulted in recovery of starting material.
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