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Oxazoles Are Masked Carboxyls That Activate Ortho-Leaving Groups in Nucleophilic Aromatic Substitution[#]

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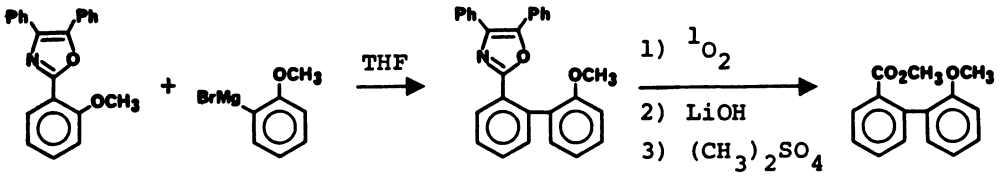
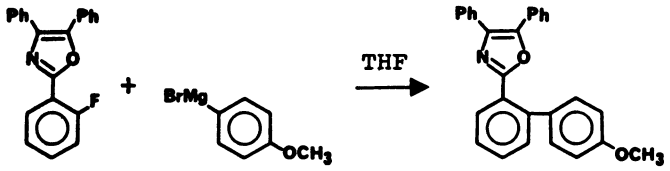
Oxazoles substituted in their 2-positions with 2-methoxy-, 2-fluoro-, or 2,6-difluorophenyl groups, and in their 4,5-positions with methyls or phenyls, were treated with ArMgBr or ArLi to give substituted biphenyl or terphenyl products. The oxazole groups were subsequently converted to esters, acids, or amides. These reactions provide a new unsymmetrical aryl-aryl coupling synthon.

Of the few methods available for unsymmetric aryl-aryl bond formation, the Meyers' method[1] of arylating o-fluoro- or o-methoxyphenyloxazolines by ArLi or ArMgBr is among the most useful. We report here that the oxazole group similarly activates attached phenyl groups toward nucleophilic aromatic substitution. Oxazoles 1, 4, 6, 9, and 12 were prepared in 59-41% isolated yields from the appropriate esters of acetoin or benzoin by heating them with NH_4OAc-AcOH.[2] The arylation reactions of 1, 4, 6, 9, and 12 to give biphenyl or terphenyl compounds 2, 5, 7, 10, and 13, respectively, occurred in 100-54% yields. The aryl Grignard readily displaced either methoxide or fluoride, but only fluoride was displaced by the aryllithium (displacement of methoxide by aryllithium was not attempted). The o-$CH_3OC_6H_4Li$ reagent was prepared by direct lithiation of anisole by BuLi. Attempts to displace fluoride from 2-[4-fluorophenyl]-4,5-diphenyloxazole with o-$CH_3OC_6H_4Li$ or o-$CH_3OC_6H_4MgBr$ gave no reaction. Thus the rate-limiting transition state free energies for the arylations appear to be lowered by intramolecular chelation of the metal by the oxazole.

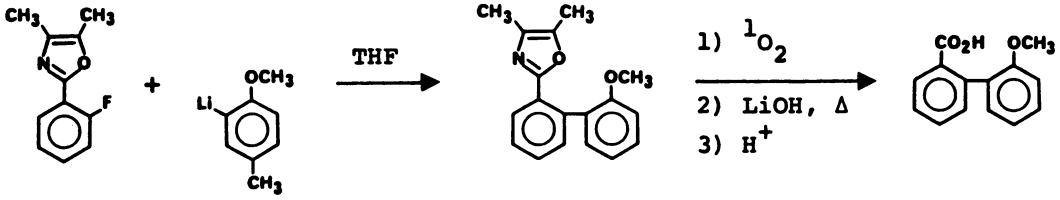
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



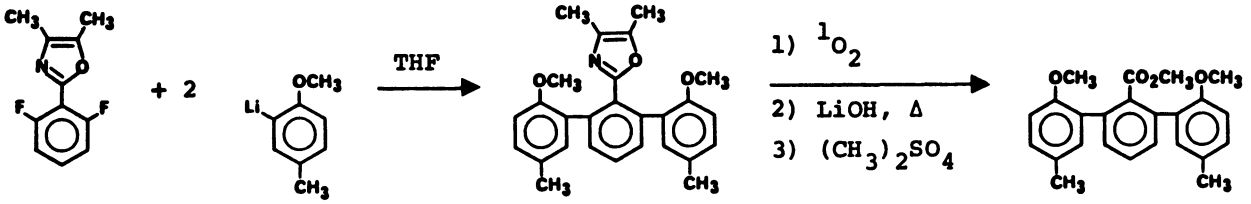
1, 41% 2, 100% 3, 30%



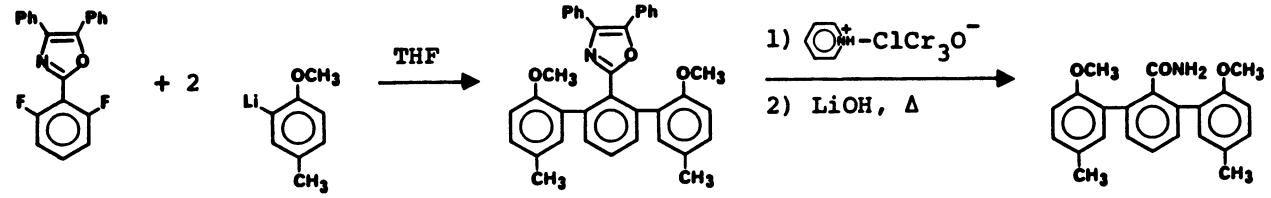
4, 59% 5, 94%



6, 41% 7, 59% 8, 54% + 16% of amide



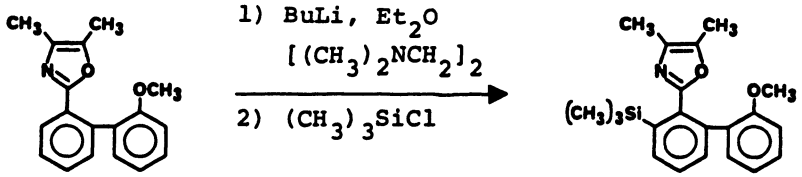
9, 44% 10, 54% 11, 15%



12, 51% 13, 65% 14, 69%

The oxazole serves both as an activating group for nucleophilic aromatic substitution and as a masked carboxyl group. Cleavage of the oxazole rings of 2, 7, and 10 by a modified Wasserman method[3] ($^1O_2$, hν, tetraphenylporphyrin, $Cl_2FCCFCl_2$) led to $(RCO)_2NCOAr$ amides which were hydrolyzed to their acids. Acid 8 (from 7, 54%) was characterized. The acids from 2 and 10 were esterified to provide 3 and 11 in 30 and 15% yields, respectively. Better results were obtained by oxidative cleavage with pyridinium chlorochromate in CH_2Cl_2 of 2-aryl-4,5-diphenyloxazole 13, followed by basic hydrolysis to provide amide 14 (69%).

Metallation of 7 with BuLi, followed by treatment of the organometallic with $(CH_3)_3SiCl$ gave 15 (45%, plus starting material), identified by a NOE experiment (^1H NMR irradiation of the CH_3O hydrogens enhanced the aryl doublet). These new reactions taken in sum provide new synthetic pathways leading to substituted polyaryl compounds useful in the design of new host compounds for complexation experiments.[4]



7 15, 45%

The procedures are illustrated by the following syntheses of 12, 13, and 14. A dry flask was purged with N_2 and charged with 600 mL of dry THF, 31.8 g (200 mmol) of 2,6-difluorobenzoic acid, 46.2 g (220 mmol) of dicyclohexylcarbodiimide, 47.1 g (220 mmol) of benzoin, and 3.1 g (25 mmol) of dimethylaminopyridine. The mixture was stirred under N_2 for 12 h and filtered. THF was distilled and the remaining liquid was dissolved in CH_2Cl_2 and washed with 5% HCl, $NaHCO_3$, and brine. The organic layer was evaporated to dryness under reduced pressure to give a yellow solid. The solid was dissolved in 200 mL of HOAc, and 39 g (500 mmol) of NH_4OAc was added. After refluxing for 12 h, the solution was cooled and 500 mL of water was added. The solution was extracted with CH_2Cl_2 and the organic layer was concentrated in vacuo. Purification was achieved by chromatography on 1300 g of silica, eluted with 50% hexanes-50% CH_2Cl_2 to give a white crystalline solid, 12, in 51% yield. (It was later found that these compounds could be purified by sublimation.)

To a dry flask purged with N_2 and charged with dry THF was added 3.8 mL (30 mmol) of p-methylanisole, followed by 12.1 mL (30 mmol) of 2.4 M n-BuLi via syringe. After stirring for 12 h, 1.0 g (3 mmol) of 2-[2,6-difluorophenyl]-4,5-diphenyloxazole (12) in THF was added. The reaction appeared complete by TLC after 12 h. The reaction was quenched with water, and the THF was distilled. Diethyl ether was added and the layers were separated. The Et_2O layer was washed with brine, dried, filtered, and evaporated to give a brown oil. The oil was chromatographed on 50 g of silica with CH_2Cl_2 to give a foam, 13, in 65% yield.

The oxazole, 13, was oxidized by method of Corey.[5] The reaction mixture was refluxed for two days and excess pyridinium chlorochromate had to be added. The isolated product was dissolved in 1:3 water/methanol, LiOH was added, and the mixture was refluxed for 24 h. The mixture was acidified and extracted with Et_2O. The Et_2O layer was washed with brine, dried, filtered, and the solvent distilled. Chromatography of this material on silica with 20% EtOAc-80% CH_2Cl_2 afforded the amide, 14, in 69% yield. All new compounds gave C and H analyses within 0.3%, the expected ^1H NMR and mass spectra, and when crystalline, gave sharp melting points.

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References

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