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ONE-STEP SYNTHESIS OF OXAZOLES FROM KETONES AND NITRILES USING COPPER(II) TRIFLUOROMETHANESULFONATE AS A KEY REAGENT

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Oxazoles were prepared in one step from ketones and nitriles using copper(II) trifluoromethanesulfonate under acid catalysis.

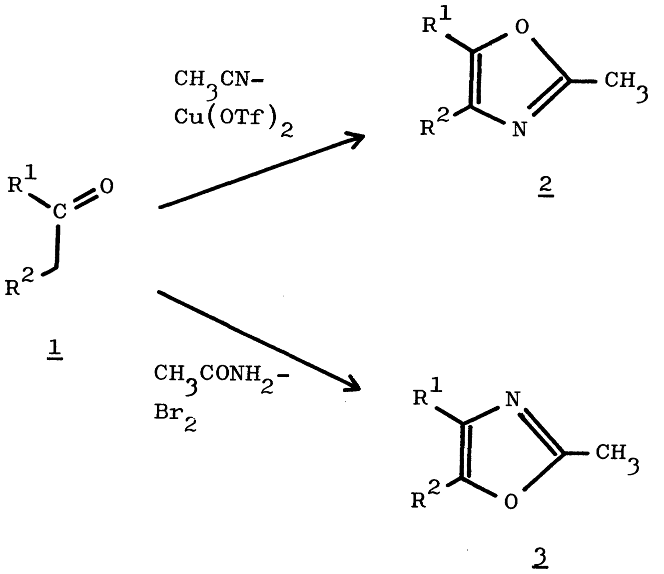
It is well documented that copper(II) ion functions as a single-electron oxidant.1) As an example copper(II) chloride is known to oxidize a ketone to a corresponding α-chloro ketone through the single-electron transfer mechanism.2) In the course of our studies on the metal-catalyzed organic reactions, we found that metal trifluoromethanesulfonate (triflate) exhibited a unique characteristic due to the extremely stabilized nature of the anion.3) These findings induced us to examine the oxidative reaction of ketone by copper(II) triflate in the hope that some species other than the counter anion of the copper(II) salts could be brought into reaction by adding an appropriate compound in the reaction system. We found now that nitrile was a suitable substrate for this purpose.

When an acetonitrile solution of a ketone 1 was refluxed for 2 h with two equivalents of copper(II) triflate and catalytic amount of p-toluenesulfonic acid, the corresponding oxazole 2 was obtained as a sole product. The results are

Table 1. Yields of Oxazoles

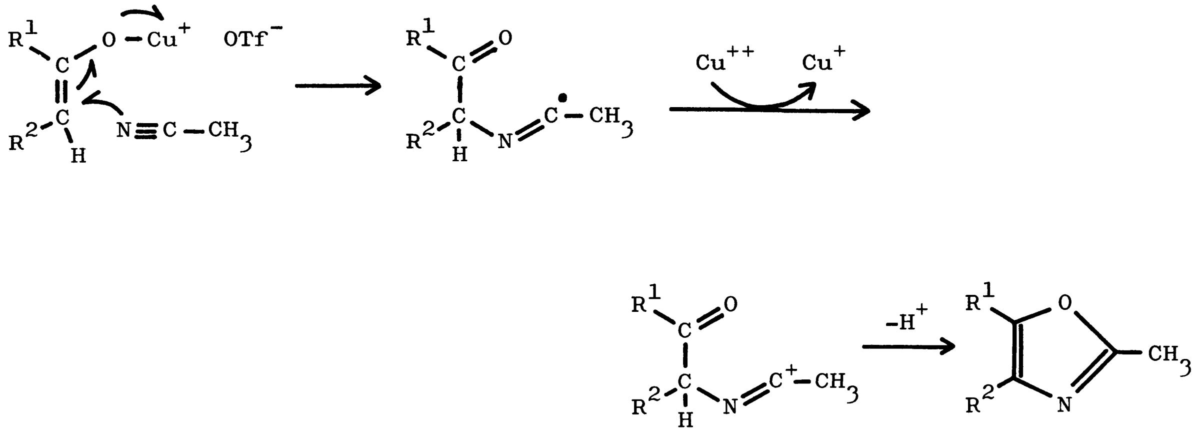
Entry	Ketone 1		Oxazole 2 (%)
	R^1	R^2	
a	CH_3	CH_3	32
b	CH_3	C_2H_5	43
c	CH_3	$i\text{-}C_3H_7$	55
d	CH_3	$n\text{-}C_4H_9$	51
e	CH_3	C_6H_5	96
f	$n\text{-}C_3H_7$	C_2H_5	47
g	C_6H_5	CH_3	70
h	Diisopropyl ketone		24a)

a) Product is 2,4,4-trimethyl-5-isopropylidene-2-oxazoline.



summarized in Table 1. The poorer yields in cases of the lower homologues might be due to the partial evaporation of the products during isolation. The products 2e and 2g were identical with the authentic samples,$^{4)}$ and the structures of the other products were assigned from the NMR and IR spectra. When the reaction was carried out with copper(II) chloride or bromide, only α-halogenation occurred even in acetonitrile, and no trace of the oxazoles was identified in the products. The copper(II) triflate-catalyzed reaction evidently proceeded with the reduction of copper(II) to copper(I), because the aqueous layer after the workup was colorless, which became deep blue upon the addition of ammonia and air blowing. When the reaction was carried out in methanol, instead of acetonitrile, the starting ketone was recovered unchanged. In cases of methyl ketones 1a - 1e, the reaction always took place at the position opposite to the methyl group. Methyl ketones which have no enolizable proton at this position, such as acetophenone and pinacolone, did not undergo the present reaction.

The present reaction may proceed with a two-fold single-electron oxidation by copper(II) ion as shown in the following scheme. Since the present reaction, if carried out in the absence of p-toluenesulfonic acid, started only after a various extent of induction period ranging from few minutes to a couple of hours, we speculated the involvement of the enolization as the primary step. Expectedly the induction period was eliminated by the addition of the protonic acid to the reaction system. Usually an oxazole 3 can be synthesized from a ketone and an amide either directly using bromine as an oxidant or indirectly via an α-halogenated ketone.$^{4)}$ From the synthetic view point, the present reaction using copper(II) triflate is notable in that it produces the oxazole which is an isomer to that obtained by these conventional methods, thus complementing the methods of the oxazole synthesis.



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