Pergamon

Tetrahedron Letters, Vol. 38, No. 52, pp. 8959-8960, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10362-8

A Novel and Direct Synthesis of 2-Alkyl-5-Aryl Disubstituted Oxazoles

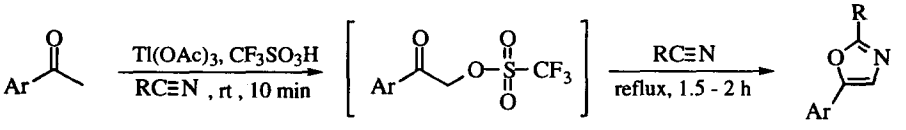
Jong Chan Lee* and Taiyoung Hong

Department of Chemistry, Chung-Ang University,
Seoul, 156-756, Korea

Abstract: A direct and efficient method for the preparation of 2-alkyl-5-aryl disubstituted oxazoles was realized by reaction of aromatic α-methyl ketones with various aliphatic nitriles in the presence of $Tl(OTf)_3$. © 1997 Elsevier Science Ltd.

Oxazoles are important constituent in biologically active natural products and served as versatile starting materials in synthetic transformations.[1] Although many good general methods are available for the preparation of oxazoles, little has been known for direct synthesis of oxazoles from ketones. Oxazole synthesis is usually accomplished through indirect methods which utilized α-halo ketones[2], α-diazo ketones[3], or α-azido ketones[4] as precursors. Among others, 2-alkyl-5-aryl disubstituted oxazole can be prepared from the reaction of (Z)-β-(acyloxy)vinyl azides with triethyl phosphite.[4a] But up to now the only previous example of direct transformation of ketones to oxazoles was the reaction of ketones with acetonitrile in the presence of $Cu(OTf)_2$ and p-TsOH.[5] However, this method was unsuccessful to give 2,5-disubstituted oxazoles because the oxazole formation didn't work for α-methyl ketones at given reaction conditions.

Herein, we report a new and direct method for conversion of aromatic α-methyl ketones to the corresponding oxazoles by use of the reaction of ketones with thallium(III) triflate (generated in situ by reaction of thallium(III) acetate with trifluoromethanesulfonic acid) in aliphatic nitriles. Various oxazoles were prepared



in high yields as summarized in Table 1. The reactions were completed by heating at reflux for 1.5 - 2 h and clean in all cases. The steric influence of nitriles had little effect on the efficiency of the oxazole formation. Furthermore, the utility of present method was demonstrated in the successful preparation of 2-cyclopropyl-5-phenyloxazole (77 % yield) and 2-methoxymethyl-5-phenyloxazole (60 % yield). Probably the reaction of α-keto triflates with nitriles proceeded via nitrilium salts formation as proposed by Meyers.[6] It has been reported that thallium(III) sulfonates can efficiently mediate α-sulfonyloxylation of ketones.[7] Thus, the formation of α-keto triflate intermediates can be reasonably explained. Due to the triflate's much better leaving ability than halide, α-keto trifalte react rapidly with nitrile as it forms without assistance of Lewis acid to give oxazoles.

Table 1. Yields of Oxazoles Prepared.

	Yield[a] (%)			
	R = CH_3	R = CH_2CH_3	R = $CH_2CH_2CH_3$	R = $(CH_3)_2CH$
Ar = Ph	83	79	86	81
Ar = *p*-$CH_3C_6H_4$	79	81	83	83
Ar = *p*-$CH_3OC_6H_4$	85	83	85	84
Ar = *p*-ClC_6H_4	86	77	87	82
Ar = 	71	74	78	79

[a] Yields of isolated and purified products.

Although the reaction worked well for aliphatic nitriles, the reaction of acetophenone with benzonitrile afforded 2,5-diphenyloxazole in 35 % yield at the present reaction conditions. The lower yield can be attributed to the high stability of benzylic cation intermediate.

In summary, the method described herein provides an excellent approach for the direct transformation of 2-alkyl-5-aryl disubstituted oxazoles.[8] The application of the present method for synthesis of biologically active oxazolylindole alkaloids is currently underway.

Acknowledgment: This work was supported by Basic Science Research Institute Program (BSRI-97-3450), Ministry of Education, Korea.

References and Notes

1. (a) Pattenden, G. *J. Heterocyclic Chem.* **1992**, *29*, 607. (b) Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1. (c) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (d) Lewis, J. R. *Nat.Prod. R.* **1995**, *12*, 135. (e) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192.
2. (a) Bredereck, H.; Gompper, R. *Chem. Ber.* **1954**, *87*, 700. (b) Bredereck, H.; Gompper, R.; Reich, F. *Chem. Ber.* **1960**, *93*, 1389. (c) Lora-Tamayo, M.; Madronero, R. ; Leipprand, H. *Chem. Ber.* **1964**, *97*, 2230.
3. (a) Kitatani, K; Hiyama, t.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1647. (b) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657. (c) Doyle, K. J.; Moody, C. J. *Synthesis*, **1994**, 1021. (d) Ibata, T.; Fukushima, K. *Chem. Lett.* **1992**, 2197.
4. (a) Takeuchi, H.; Yanagida, S.; Ozaki, T.; Hagiwara, S.; Eguchi, S. *J. Org. Chem.* **1989**, *54*, 431. (b) Molina, P.; Fresneda, P. M.; Almendros, P. *Synthesis*, **1993**, 54.
5. Nagayoshi, K.; Sato, T. *Chem. Lett.* **1983**, 1355.
6. Meyers, A.I.; Sircar, J. C., in *The Chemistry of the Cyano Group* ; Rappoport, Z., Ed; Interscience, New York, **1970**, p. 341.
7. (a) Khanna, M. S.; Garg, C. P.; Kapoor, R. P. *Tetrahedron Lett.* **1992**, *33*, 1495. (b) Khanna, M. S.; Garg, C. P.; Kapoor, R. P. *Synlett*, **1992**, 393.
8. A typical procedure is as follows: To a stirred solution of the thallium(III) acetate (0.572 g, 1.5 mmol) in CH_3CN (40 mL) was added CF_3SO_3H (0.675 g, 4.5 mmol) and the mixture was stirred at room temperature for 10 min. To the reaction mixture acetophenone (0.120 g, 1.0 mmol) in CH_3CN (20 mL) was added and stirring was continued at reflux for 1.5 h. After evaporation of the solvent, the residue was extracted with CH_2Cl_2 (2 x 30 mL), washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was flash chromatograped on silica gel using ethyl acetate-hexa -ne (1:2) as eluent to give 2-methyl-5-phenyloxazole (0.132 g, 83 %) as white solid.

(*Received in Japan* 2 *September* 1997; *revised* 6 *October* 1997; *accepted* 9 *October* 1997)