Category

Synthesis of Heterocycles

Key words

chromones

O-arylation

S_NAr reaction

J. ZHAO, Y. ZHAO, H. FU* (TSINGHUA UNIVERSITY, BEIJING, P. R. OF CHINA)

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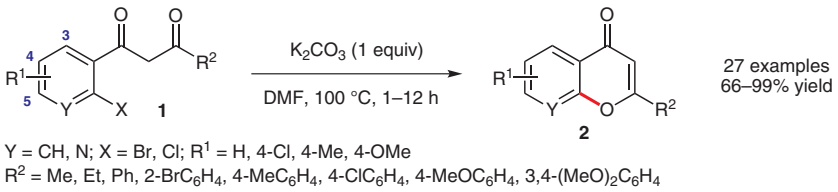
Transition-Metal-Free S_NAr-Type Synthesis of Chromones



Y = CH, N; X = Br, Cl; R^1 = H, 4-Cl, 4-Me, 4-OMe
R^2 = Me, Et, Ph, 2-BrC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_4$

Significance: This report represents a *caveat* publication. Aiming to develop a copper-catalyzed synthesis of chromones **2** via an intramolecular Ullmann O-arylation of (*ortho*-halophenyl)propane-1,3-diones **1**, Fu and co-workers, to their credit, carried out a control experiment without a copper catalyst. This led to the discovery that the O-arylation proceeded more efficiently without the aid of a transition metal, thus representing a normal intramolecular S_NAr process. The reaction was carried out under basic conditions (K_2CO_3, Na_2CO_3, K_3PO_4) in polar aprotic solvents (DMF, DMSO, NMP); the combination of K_2CO_3 and DMF giving the best results. Surprisingly, aryl bromides were more reactive than aryl chlorides, although both gave good to high yields of chromone products. Starting materials **1** with R^2 = aryl groups gave higher yields compared to R^2 = aliphatic ones. Also, R^1 = EDG showed lower reactivity. Control experiments showed that 1) oxygen has no effect on the reaction and 2) the reaction does not proceed through a radical pathway. Surprisingly, the simple intermolecular O-arylation of 1-bromo-2-nitrobenzene with phenol under the same conditions failed.

Comment: Aryl ethers are classically prepared by copper-mediated Ullmann and palladium-catalyzed Buchwald–Hartwig coupling reactions of aryl halides with phenols. Intramolecular metal-catalyzed O-arylation couplings have been applied to the synthesis of various heteroaromatics including chromones (Q. Yang, H. Alper *J. Org. Chem.* **2010**, *75*, 948). Chromones are ubiquitous in Nature, especially in the class of plant secondary metabolites, for example flavonoids (see Book below). Metal-free strategies to chromones often suffer from harsh conditions, poor substituent tolerance and low yields (see Review below). A recent synthesis of chromones involves the sequential intramolecular anionic *ortho*-Fries rearrangement–Michael addition of 2-but-2-ynoyl aryl *O*-carbamates (T. K. Macklin, J. Panteleev, V. Snieckus *Angew. Chem. Int. Ed.* **2008**, *47*, 2097). The present method represents a convenient and efficient access to chromones **2** starting from **1** prepared via a simple Claisen condensation between methyl *ortho*-halobenzoate derivatives and ketones. This work teaches the necessity for execution of control experiments in all studies concerned with transition-metal-catalyzed C–C, C–O, and C–N couplings.

Book: J. B. Harborne, H. Baxter *The Handbook of Natural Flavonoids*, Vol. 1; John Wiley & Sons: Chichester, UK, **1999**.

Review: N.-G. Li, Z.-H. Shi, Y.-P. Tang, H.-Y. Ma, J.-P. Yang, B.-Q. Li, Z.-J. Wang, S.-L. Song, J.-A. Duan *J. Heterocycl. Chem.* **2010**, *47*, 785-798.

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