

A Mild, Efficient Approach to 3-Acyfurans: A Short Synthesis of Perilla Ketone

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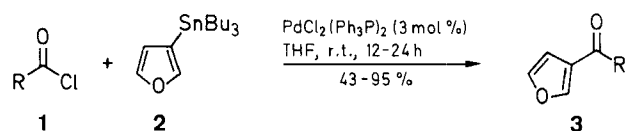
Dedicated in memory of the late Professor J. K. Stille

Several 3-acylfurans **3** were prepared in excellent yield using a one-pot procedure involving the palladium-catalyzed cross-coupling of commercially available acid chlorides with tributyl(3-furyl)stannane **2** at *room temperature*.

Furans possessing 3-substituents, while naturally abundant,¹ have proven to be non-trivial synthetic targets. Several multi-step synthetic approaches to 3-acylfurans have been described,^{2–7} but few have demonstrated broad synthetic utility. In this paper, we propose an efficient, one-step synthesis of 3-acylfurans utilizing readily available reagents.

The direct acylation of the furan heterocycle using Friedel–Crafts methodology is known to occur exclusively at the 2- and 5-positions in good yield.⁸ A single example of a direct acylation at the 3-position of furan was recently reported by Gilchrist.⁹ In that example, a 3-bromozinc furan (prepared from the 3-lithiofuran) was

coupled to benzoyl bromide using 4 mol% tetrakis(triphenylphosphine)palladium(0) in refluxing tetrahydrofuran. The 3-benzoylfuran was obtained in a modest (32%) yield. We perceived that such a direct acylation might more efficiently be achieved using Stille-type organotin/acid chloride coupling methodology.¹⁰ Using a modified procedure, we have found that 3-acylfurans are efficiently generated by palladium catalyzed (3 mol%) coupling of inexpensive and commercially available acid chlorides with tributyl(3-furyl)stannane¹¹ in tetrahydrofuran at *room temperature*. Surprisingly, this is the first application of this type of methodology in the 3-acylation of furans.¹² In the absence of the palladium catalyst, no reaction occurs. Yields are generally excellent (86–95%) with the exception of the modest 43% for the extremely volatile 3-acetylfuran (Table).



1,3	R	1,3	R
a	Me	d	2-thienyl
b	(CH ₂) ₇ CH ₃	e	2-furyl
c	Ph		

Table. 3-Acylfurans **2a-e** Prepared

Product	Yield ^b (%)	mp (°C) ^c (solvent)	Lit. mp (°C)
2a	43	47–49 (hexane)	50 ¹⁹
2b	86	41–42 (pentane)	42–45 ²⁰
2c	91	38–39 (pentane)	39–40 ²¹
2d	95	46–48 (Et ₂ O/hexane)	46 ²²
2e	95	57–59 (hexane)	56–57 ²

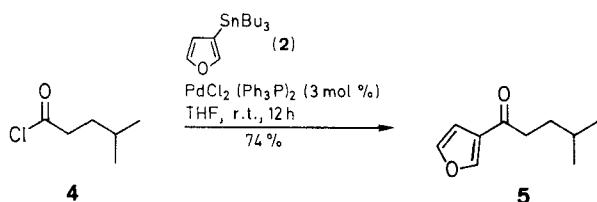
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^a The ¹H-NMR s were identical to literature reports.

^b Yield of isolated product.

^c Uncorrected.

To further highlight the utility of this procedure, we chose to synthesize perilla ketone **5**, a naturally occurring terpene isolated from the mint plant *Perilla frutescens*.¹³ Several syntheses of perilla ketone have been reported,^{3–5,14–17} but all are multi-step approaches with overall yields ranging from 14–78%. Using our modified procedure, we have directly synthesized perilla ketone in a single step in 74% yield.¹⁸



This methodology illustrates a facile, single step synthesis of simple 3-acylfurans that is quite amenable to large scale synthesis. This synthetic method should prove useful in the synthesis of more complex and biologically interesting molecules.

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. The ¹H-NMR spectra were performed on a General Electric QE-300 using CDCl₃ with TMS as the internal standard. THF was dried via distillation from sodium/benzophenone.

3-Acylfurans **2a-e** and **5**; General Procedure:

To a 0.5 M solution of the appropriate acid chloride in dry THF (14 mL) is added tributyl(3-furyl)stannane¹¹ (1.1 equiv) and 3 mol% of PdCl₂(PPh₃)₂.^{2,3} The yellow suspension is stirred under N₂ for 12–24 h by which time the mixture has become completely homogeneous. The THF is removed under vacuum, and the crude mixture is subjected to medium pressure liquid chromatography (MPLC, Kieselgel 60; 5:1 hexane/EtOAc) monitored by UV (260 nm). Purity is evaluated by TLC, 300 MHz ¹H-NMR, and comparison of the melting points with literature values.

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