# A novel one-pot three-component synthesis of 3-halofurans and sequential Suzuki coupling†

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**A novel sequence of Sonogashira coupling and electrophilic addition to an ynone, with concomitant deprotection and cyclocondensation, opens a new one-pot synthesis of 3-halofurans; the method can be readily elaborated to a new sequential Sonogashira–addition–cyclocondensation–Suzuki reaction to furnish 2,3,5-trisubstituted furans in a one-pot fashion.**

Furans are ubiquitous structural units in numerous natural products,[1] in pharmaceuticals,[2] and even in photonic chromophores.[3] Among various syntheses of furans,[4] the two major approaches[5] are either based upon the construction of the furan ring starting from acyclic precursors[6] or substitution reactions on the furan core. In particular, by regiospecific substitutions, halofurans are ideal starting materials, either as electrophiles in cross-coupling reactions[7] or, *via* halogen–metal exchange, as nucleophiles for subsequent electrophilic trapping.[8] However, efficient and concise syntheses of 3-substituted halofurans are still a methodological challenge.[9,10] As part of our program directed to develop new one-pot multi-component heterocycle syntheses initiated by transition metal catalyzed alkyne coupling,[11] here, we communicate a novel one-pot three-component synthesis of 3-halofurans and sequential cross-coupling, still in a one-pot fashion.

Recently, we have developed a modification of the Sonogashira coupling of acid chlorides and terminal alkynes to give alkynones,[11] where *only one stoichiometric equivalent* of triethylamine, necessary as hydrochloric acid scavenging base, is applied. Therefore, the reaction medium becomes *essentially base free*, now setting the stage for acid catalyzed consecutive steps. Ynones possess an enormous potential as key intermediates in heterocycle synthesis.[12] Hence, we reacted benzoyl chloride (**1a**) and the tetrahydropyranyl propargyl ether (**2a**) under modified Sonogashira conditions, followed by the addition of NaCl and *p*-tolylsulfonic acid (PTSA) in methanol, to give, through the intermediacy of an γ-hydroxy alkynone,[13] 4-chloro-2-phenylfuran (**3a**) in 63% yield (Scheme 1).

This novel sequence can be rationalized as a cross-coupling furnishing a THP-protected 3-hydroxy alkynone that is solvolyzed under acid catalysis to give rise to the γ-hydroxy alkynone. Acid-assisted Michael addition of HCl and subsequent cyclocondensation conclude the three-component sequence to give the 4-chlorofuran **3a**.

† Electronic supplementary information (ESI) available: experimental procedures and characterization for compounds **3** and **5**. See http://www.rsc.org/suppdata/cc/b5/b502324f/

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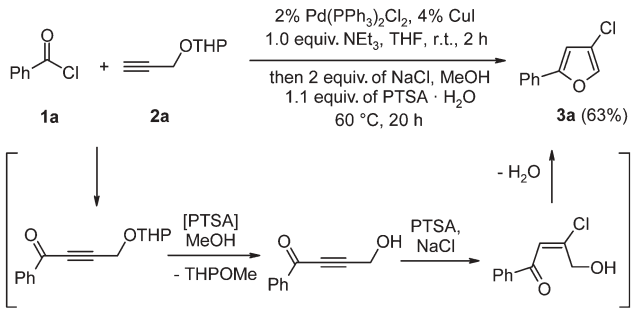
According to these optimal conditions, with the extension to using sodium iodide as a halide source, various acid chlorides **1** and tetrahydropyranyl propargyl ethers **2** can be successfully transformed into 3-halofurans **3** in a one-pot coupling–addition–cyclocondensation sequence (Scheme 2, Table 1).[14]

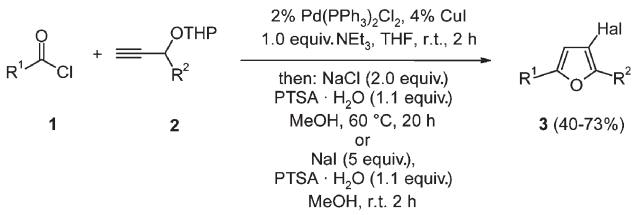
The structure of the 3-halofurans **3** is unambiguously supported by an X-ray structure analysis for **3i** (Fig. 1).‡

Methodologically, this new one-pot three-component synthesis of 3-halofurans proceeds efficiently under mild conditions with a wide variety of electronically diverse acid chlorides. Applying NaI as a halide source leads to even milder reaction conditions and shorter reaction times, now giving extremely valuable 3-iodofurans. Therefore, due to the acid sensitivity of iodofurans, this methodology has significant advantages over existing protocols using HI as an acid.

Finally, as a showcase for the highly topical field of sequential catalysis[15] we probed a sequential Sonogashira–addition–cyclocondensation–Suzuki reaction where the same catalyst system should be applied for two consecutive, significantly different, cross-coupling reactions in the same reaction vessel. Therefore, upon consecutive reactions of acid chlorides **1** and tetrahydropyranyl propargyl ethers **2**, NaI and PTSA, and addition of 1.05 equiv. of




**Scheme 1** Coupling–addition–cyclocondensation sequence to 4-chlorofuran **3a**.




**Scheme 2** Coupling–addition–cyclocondensation synthesis of 3-halofurans **3**.

**Table 1** One-pot three-component synthesis of 3-halofurans **3**

| Entry | Acid chloride **1** | Alkyne **2** | 3-Halofuran **3** (yield) |
|---|---|---|---|
| 1[a] | $R^1$ = Ph (**1a**) | $R^2$ = H (**2a**) | **3a** ($R^1$ = Ph , $R^2$ = H, Hal = Cl, 63%) |
| 2[a] | $R^1$ = *p*-$MeOC_6H_4$ (**1b**) | **2a** | **3b** ($R^1$ = *p*-$MeOC_6H_4$, $R^2$ = H, Hal = Cl, 71%) |
| 3[a] | **1a** | $R^2$ = Et (**2b**) | **3c** ($R^1$ = Ph, $R^2$ = Et, Hal = Cl, 70%) |
| 4[a] | $R^1$ = 2-thienyl (**1c**) | **2b** | **3d** ($R^1$ = 2-thienyl, $R^2$ = Et, Hal = Cl, 59%) |
| 5[a] | $R^1$ = PhCH=CH (**1d**) | **2b** | **3e** ($R^1$ = PhCH=CH, $R^2$ = Et, Hal = Cl, 73%) |
| 6[a] | $R^1$ = 1-cyclohexenyl (**1e**) | **2a** | **3f** ($R^1$ = 1-cyclohexenyl, $R^2$ = H, Hal = Cl, 64%) |
| 7[b] | **1a** | **2a** | **3g** ($R^1$ = Ph, $R^2$ = H, Hal = I, 63%) |
| 8[b] | **1b** | **2a** | **3h** ($R^1$ = *p*-$MeOC_6H_4$, $R^2$ = H, Hal = I, 63%) |
| 9[b] | $R^1$ = *p*-$NO_2C_6H_4$ (**1f**) | **2a** | **3i** ($R^1$ = *p*-$NO_2C_6H_4$, $R^2$ = H, Hal = I, 40%) |
| 10[b] | **1a** | **2b** | **3j** ($R^1$ = Ph, $R^2$ = Et, Hal = I, 72%) |

[a] 2.0 equiv. of NaCl, 60 °C, 20 h. [b] 5 equiv. of NaI, r.t., 2 h.

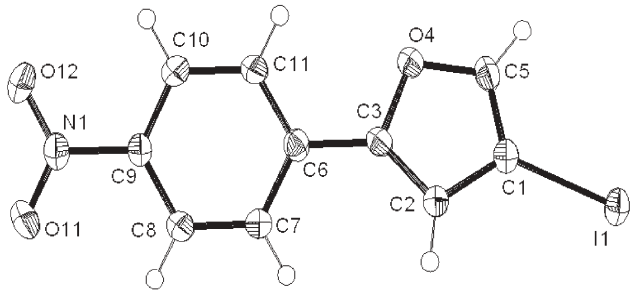
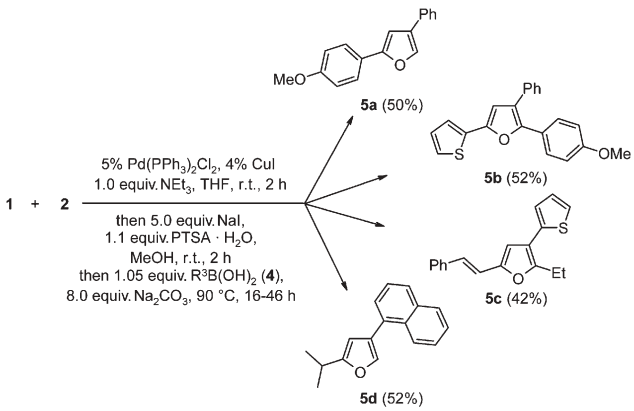



**Fig. 1** Molecular structure of **3i** ($R^1$ = *p*-$NO_2C_6H_4$, $R^2$ = H, Hal = I). Only 1 of 4 independent molecules is shown. The enumeration is adjusted.




**Scheme 3** Sequential Sonogashira–addition–cyclocondensation–Suzuki synthesis of substituted 3-arylfurans **5**.

boronic acids **4** and sodium carbonate, the substituted 3-arylfurans **5** were obtained in decent yields (Scheme 3).[16]

The new one-pot Sonogashira–addition–cyclocondensation–Suzuki synthesis of substituted 3-arylfurans **5** proceeds in reasonable yields that are almost comparable (one-pot sequence to **5a**: 50%) with a stepwise procedure (overall yield of **5a**: 45%).

In conclusion, we have developed a novel consecutive three-component coupling–addition–cyclocondensation synthesis of 3-halofurans, highly versatile building blocks in organic synthesis. In addition, a new sequential Sonogashira–addition–cyclocondensation–Suzuki multi-component furan synthesis was readily elaborated as a new diversity-oriented consecutive multi-component access to substituted 3-arylfurans. Studies addressing the scope of this sequence to enhance molecular diversity are currently under investigation.

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## Notes and references

‡ Crystal data for **3i**: $C_{10}H_6INO_3$, $M$ = 315.1, triclinic, space group $P\bar{1}$, $a$ = 8.2679(1), $b$ = 11.0675(1), $c$ = 22.2477(2) Å, $\alpha$ = 84.927(1)°, $\beta$ = 83.749(1)°, $\gamma$ = 88.385(1)°, $V$ = 2015.39(4) Å$^3$, $T$ = 200(2) K, $Z$ = 8, $\rho$ = 2.077 g cm$^{-3}$, crystal dimensions 0.50 × 0.34 × 0.30 mm$^3$, Mo $K_\alpha$ radiation, $\mu$ = 3.162 mm$^{-1}$, $\lambda$ = 0.71073 Å. There are four independent molecules in the asymmetric unit. Data were collected on a Bruker Smart APEX diffractometer and a total of 9160 of the 20833 reflections were unique [$R$(int) = 0.0201]. Refinement on $F^2$, $wR_2$ = 0.049 (observed reflections), $R_1$ = 0.021 for [$I > 2\sigma(I)$]. CCDC 260725. See http://www.rsc.org/suppdata/cc/b5/b502324f/ for crystallographic data in CIF or other electronic format.

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14 **Typical procedure (compound 3j):** 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$ and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF. Then 141 mg (1.0 mmol) of **1a**, 168 mg (1.0 mmol) of **2b**, and 0.14 mL (1.00 mmol) of triethylamine were successively added to the solution and the mixture was stirred for 2 h at room temperature. Then 750 mg (5.00 mmol) of sodium iodide, 209 mg (1.10 mmol) of *p*-tolylsulfonic acid monohydrate and 3 mL of methanol were added and stirring at room temperature was continued for 2 h. After aqueous work up with a saturated solution of $NaHCO_3$ and $Na_2SO_3$ and chromatography on neutral aluminium oxide (hexane–ethyl acetate 9:1–20:1), 215 mg (72%) of pure **3j** were obtained as a light yellow oil. $^1$H NMR (acetone-$d_6$, 300 MHz): $\delta$ 1.26 (t, $J$ = 7.7 Hz, 3 H), 2.76 (q, $J$ = 7.7 Hz, 2 H), 6.89 (s, 1 H), 7.26–7.32 (m, 1 H), 7.38–7.45 (m, 2 H), 7.66–7.71 (m, 2 H). $^{13}$C NMR (acetone-$d_6$, 75 MHz): $\delta$ 12.8 ($CH_3$), 21.6 ($CH_2$), 63.9 ($C_{quat}$), 113.6 (CH), 124.2 (CH), 128.5 (CH), 129.7 (CH), 131.0 ($C_{quat}$), 154.4 ($C_{quat}$), 158.1 ($C_{quat}$). Calc. HRMS for $C_{12}H_{11}IO$: 297.9855. Found: 297.9861.
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16 **Typical procedure (compound 5a):** 35 mg (0.05 mmol) of $Pd(PPh_3)_2Cl_2$ and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF. Then 171 mg (1.00 mmol) of **1b**, 141 mg (1.00 mmol) of **2a**, and 0.14 mL (1.00 mmol) of triethylamine were successively added to the solution and the mixture was stirred for 2 h at room temperature. Then 750 mg (5.00 mmol) of sodium iodide, 209 mg (1.10 mmol) of *p*-tolylsulfonic acid monohydrate and 3 mL of methanol were added and stirring at room temperature was continued for 2 h. Then 4 mL (8 mmol) of a 2 M solution of aqueous sodium carbonate and 128 mg (1.05 mmol) of boronic acid **4a** were added and the mixture was heated at 90 °C for 28 h. After aqueous work up and chromatography on silica gel, 115 mg (50%) of the analytically pure 2-substituted 3-phenylfuran **5a** were obtained as a colorless solid. $R_f$ = 0.42 (hexane–ethyl acetate 9:1). Mp 129 °C. $^1$H NMR (acetone-$d_6$, 300 MHz): $\delta$ 3.84 (s, 3 H), 7.02 (d, $J$ = 8.8 Hz, 2 H), 7.16 (d, $J$ = 0.7 Hz, 1 H), 7.24–7.31 (m, 1 H), 7.36–7.44 (m, 2 H), 7.63–7.68 (m, 2 H), 7.72 (d, $J$ = 8.8 Hz, 2 H), 8.02 (d, $J$ = 0.7 Hz, 1H). $^{13}$C NMR (acetone-$d_6$, 75 MHz): $\delta$ 55.6 ($CH_3$), 103.3 (CH), 115.1 (CH), 124.5 ($C_{quat}$), 126.1 (CH), 126.5 (CH), 127.8 (CH), 129.3 ($C_{quat}$), 129.6 (CH), 133.4 ($C_{quat}$), 138.6 (CH), 155.8 ($C_{quat}$), 160.4 ($C_{quat}$). EI MS [*m*/*z* (%)]: 250 ($M^+$, 100), 235 ($M^+ - CH_3$, 14), 221 ($M^+ -$ CHO, 15). Anal calc. for $C_{17}H_{14}O_2$ (250.30): C 81.58, H 5.64. Found: C 81.20, H 5.63.