Note

Silver-catalyzed direct couplings of 2-substituted furans with cyclic 1,3-dicarbonyls

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Abstract

Direct alkenylation of 2-substituted furans with cyclic 1,3-dicarbonyls by means of silver catalysis have been explored. Silver salts resulted more efficient than a variety of Lewis acids and *p*-TsOH.
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1. Introduction

C–H substitution reactions of heterocyclic derivatives are an enduring challenge for organic chemists [1]. Particular focus is devoted on developing new methods to couple electron rich arenes with carbonyl compounds [2]. We have successfully applied the catalysis by gold for the cross coupling reaction of indoles/pyrroles with 1,3-dicarbonyl compounds leading the corresponding alkenyl derivatives (Scheme 1) [3].

As an extension of our studies on this chemistry, we decided to investigate the alkenylation of furans. To the best of our knowledge the direct functionalisation of furans with 1,3-dicarbonyls has not been reported. According to the literature, the target alkenyl derivatives have been synthesized through a multistep procedure involving the conversion of 1,3-dicarbonyl compounds into their 3-alkoxy-2-alkenone derivatives which subsequently gave the final products by reacting with lithiathed furans [4]. A different route entailed the synthesis of β-furyl-α,β-enones by addition of organolithium or Grignard reagents to a resin bound β-alkoxy-α,β-enone followed by hydroly-sis. Resin bound β-alkoxy-α,β-enone could, also, be transformed into the corresponding vinyl triflates which undergo palladium-mediated couplings with orgaboron derivatives and hydrolysis to give the corresponding alkenyl furan derivatives [5]. Hereafter we report that functionalisation of 2-substituted furans can be accomplished directly through their silver-catalyzed reaction with cyclic 1,3-dicarbonyls.

2. Results and discussion

To begin our study, we imagined that the results of the gold-catalyzed alkenylation reaction of indoles/pyrroles with 1,3-dicarbonyl compounds could be extended to an analogous coupling of furans. These derivatives have been reported to hydroarylate alkynes [6], allenyl ketones [7], α,β-unsaturated carbonyl compounds [8], and imines [9] in intermolecular gold-catalyzed reactions. Moreover, cycloisomerization of alkynyl furans afforded the exo cyclization products by means of $Hg(OAc)_2 \cdot 0.1Sc(OTf)_3$ catalytic system [10]. We expected that the direct coupling would link furans to 1,3-dicarbonyl derivatives to their more nucleophilic α-position. However, by reacting 2-methylfuran (**1a**) with 1,3-cyclohexanedione (**2a**) (Scheme 2) in dichlorethane (DCE) at 80 °C in the presence of the
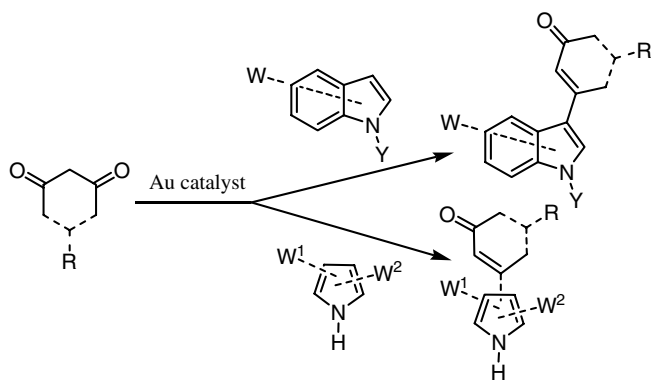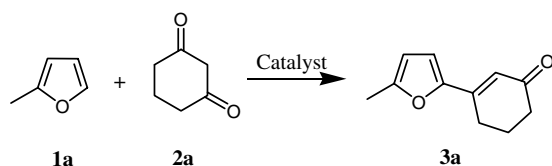
Scheme 1.

Scheme 2.

catalytic system AuBr$_3$/2AgOTf (5 mol% based on gold) we observed the regioselective formation of the coupling derivative 3-(5-methyl-furan-2-yl)-cyclohexen-2-one **3a**, but in disappointing 13% yield (Table 1, entry 1). Similarly, **3a** was isolated in low yields by using Au(III) and Au(I) catalysts (Table 1, entries 2–4, 6). Increasing the reaction temperature resulted also the formation of **3a**

Table 1
Alkenylation[a] of **1a** with **2a**

Entry	**1a/2a**	Solvent	Catalyst	Temperature (°C)/time (h)	Yield of **3a** (%)
1	0.5	DCE	AuBr$_3$/AgOTf	80/24	13
2	0.5	DCE	AuBr$_3$	80/24	–
3	0.5	MeCN	NaAuCl$_4 \cdot$ 2H$_2$O	80/24	19
4	2.0	MeCN	NaAuCl$_4 \cdot$ 2H$_2$O	120/3.5	10
5	0.5	DCE	AuBr$_3$/AgOTf	140/1	25
6	2.0	DCE	AuCl	120/3.5	–
7	2.0	DCE	Ph$_3$AuOTf	120/3.5	13
8	2.0	DCE	AuCl/AgOTf	120/3.5	57
9	0.5	DCE	AgOTf	80/24	26
10	2.0	DCE	AgOTf	80/24	51
11	3.0	DCE	AgOTf	80/24	63
12	2.0	DCE	AgOTf	120/3.5	60
13	2.0	DCE	Cu(OTf)$_2$	120/3.5	40
14	2.0	DCE	FeCl$_3 \cdot$ H$_2$O	120/3.5	23
15	2.0	DCE	ZnCl$_2$	120/3.5	12
16	2.0	DCE	*p*-TsOH	120/3.5	28
17	2.0	DCE	AgClO$_4 \cdot$ H$_2$O	120/3.5	60
18	2.0	DCE	AgClO$_4$	120/3.5	47
19	2.0	DCE	AgNTf$_2$	120/3.5	46
20	2.0	DCE	AgSbF$_6$	120/3.5	43
21	2.0	DCE	AgBF$_4$	120/3.5	30
22	2.0	DCE	AgNO$_3$	120/3.5	–
23	2.0	DCE	Ag$_2$O	120/3.5	–

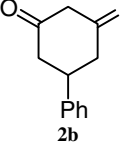[a] Yields refer to single runs, and are given for pure isolated **3a**.
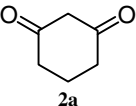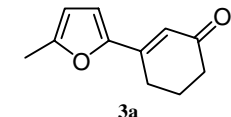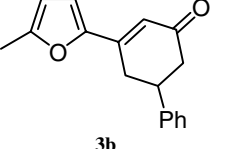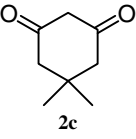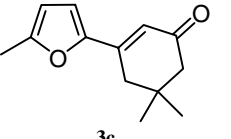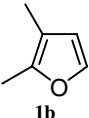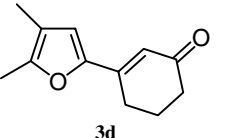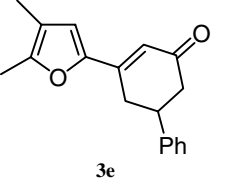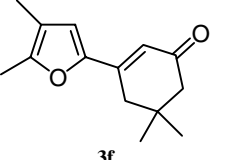
in poor yield (Table 1, entry 5). Whereas AuCl alone was unreactive (Table 1, entry 6), the combination AuCl/AgOTf led to the desired product **3a** in 57% (Table 1, entry 8). PPh$_3$AuOTf proved to catalyze the reaction, but with a far lower efficiency (Table 1, entry 7). A control experiment employing AgOTf (10 mol%) as the sole catalyst under the same reaction conditions produced **3a** in 60% yield. Besides gold derivatives, other Lewis acids such as Cu(OTf)$_2$, FeCl$_3 \cdot$ 6H$_2$O and ZnCl$_2$ resulted less efficient than AgOTf in the coupling reaction of **1a** with **2a**. In addition a catalytic amount of the Brønsted acid *p*-TsOH allowed the production of **3a**, albeit only in 28% yield. These results are in contrast with those observed in the condensation of furans with carbonyl compounds [4]. Furans have been reported to undergo a twofold condensation with carbonyl compounds and the reaction was efficiently promoted by gold as well as mercury, thallium and *p*-toluenesulphonic acid. In view of their low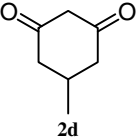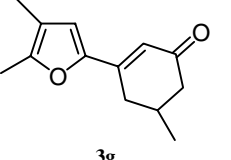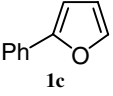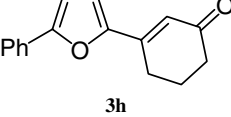 cost and simplicity we examined a variety of silver derivatives. Whereas Ag$_2$O and AgNO$_3$ resulted not effective, herein we report that other silver salts can promote the alkenylation of **1a** in satisfactory yield (Table 1, entries 17–21) and AgClO$_4 \cdot$ H$_2$O gave the same result of AgOTf. This finding is especially noteworthy as silver based catalysts have not been used extensively. They are commonly employed as innocent anion exchange agents for the *in situ* generation of cationic transition (and other) metal catalysts [11].

Only recently Ag-catalyzed reactions are emerging as important synthetic methods for a variety of organic transformations [12]. In comparison with other transition metals, silver is still in its infancy [13]. Then we set up to explore the scope of the silver-catalyzed coupling process of 2-substituted furans with other cyclic 1,3-diketones and the results are summarized in Table 2.

It is clear from our results that the silver-catalyzed reaction of 2-substituted furans with cyclic 1,3-diketones provides an alternative more simple approach to the synthesis of 2-alkenylfurans in comparison with the existing methodologies. Previously, 1,3-diketones have been reported to give a highly efficient silver-catalyzed inter- and intramolecular hydroalkylation reaction on unsaturated organic substrates [14]. By contrast, in all the cases we examined we observed only C–C coupling reaction on the carbonyl moiety. Overall the oxidative properties of silver catalysts may direct a stronger coordination than gold ones to the oxygen atom of the carbonyl function [15]. It is reasonable to assume that activation of the carbonyl group, followed by a Friedel-Crafts-type reaction could be responsible of the formation of the corresponding alkenyl derivative. The stronger activation by silver determines its better efficiency in the alkenylation of 2-substituted furans. This latter derivatives are reported to react more slowly than indoles/pyrroles with electrophilic reagents.

In conclusion, we have shown that the traditional stepwise formation of α-alkenyl furans can be replaced by one-step procedure by means of silver catalysis. Additional

Table 2
Silver-catalyzed alkenylation of 2-substituted furans[a] with cyclic 1,3-dicarbonyl compounds

Entry	HetAr-H 1	1,3-Dicarbonyl 2	Time (h)	Product 3	Yield (%)[b]
1	1a	2a	3.5	3a	60
2	1a	2b	5.5	3b	64
3	1a	2c	7.0	3c	40
4	1b	2a	1.5	3d	82
5	1b	2b	3.0	3e	88
6	1b	2c	7.5	3f	56
7	1b	2d	2.0	3g	85
8	1c	2a	2.0	3h	70[c]

[a] Reactions were carried out by using the following molar ratios and at 120 °C: 1:2:AgOTf = 2:1:0.1 in ClCH₂CH₂Cl.
[b] Yield of pure isolated product.
[c] Molar ratios: 1c:2a:AgOTf = 2:1:0.5.

advantages towards the previous reported procedures of condensations of electron rich heteroarenes with carbonyl compounds are represented by the lower toxicity of silver catalyst compared to Tl and Hg derivatives. The silver salts are more active than gold catalysts in promoting the alkenylation of furans.

3. Experimental

Temperatures are reported as bath temperature. Compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm). The products, after usual work-up, were purified by flash chromatography on silica gel (230–400 mesh) eluting with n-hexane/ethyl acetate mixtures. These solvents were distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 200 E spectrometer. EI (70 eV). Mass spectra were recorded with a Varian Saturn 2100 T GC/MS instrument and ESI accurate mass measurements were recorded with a Mass spectrometer Finnigan TSQ Quantum Ultra with accurate mass options instrument. IR were recorded with a Perkin–Elmer 683 spectrometer. Only the most significant IR absorptions are given. All starting materials, catalysts, and solvents if not otherwise stated, are commercially available and were used as purchased, without further purification. The 2-phenylfuran **1c**, was prepared by published procedure [16]. The product **3a** [17] is known and was determined using comparison of its physical and spectral data with those reported in the literature.

3.1. General procedure for the silver-catalyzed alkenylation of 2-substituted furans 1 with cyclic 1,3-dicarbonyls (2)

To a solution of the furan derivative **1** (1 mmol) in $ClCH_2CH_2Cl$ (2 mL) were added the cyclic 1,3-dicarbonyl compound **2** (2 mmol) and AgOTf or $AgClO_4 \cdot H_2O$ (0.10 mmol). The mixture was stirred at 120 °C for the appropriate time and monitored by TLC or GC–MS. After completion, the solvent was removed by evaporation. The residue was purified by chromatography on silica gel (230–400 mesh) eluting with n-hexane/ethyl acetate mixtures to afford the pure derivative **3**.

3.2. 3-(5-Methyl-furan-2-yl)-5-phenyl-cyclohex-2-enone (3b)

IR (neat): $v = 1700, 1600, 1540, 740\ cm^{-1}$. ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 2.34$ (s, 3H), 2.64–2.91 (m, 4H), 3.35–3.45 (m, 1H), 6.11 (d, $J = 3.3$ Hz, 1H), 6.49 (d, $J = 1.9$ Hz, 1H), 6.64 (d, $J = 3.3$ Hz, 1H), 7.26–735 (m, 5H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 33.1, 40.5, 44.2, 108.9, 114.4, 119.3, 126.7, 127.0, 128.7, 143.2, 146.2, 150.3, 156.0, 198.6$. MS (70 EV, EI, relative intensity): 253 [(M+1)$^+$, 100], 148 (43). ESI-HRMS calculated for $C_{17}H_{17}O_2$: 253.1229. Found: 253.1233%.

3.3. 5,5-Dimethyl-3-(5-methyl-furan-2-yl)-cyclohex-2-enone (3c)

IR (neat): $v = 1710, 1595, 1540, 760\ cm^{-1}$. ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 1.09$ (s, 6H), 2.29 (s, 2H), 2.35 (s, 3H), 2.47 (s, 2H), 6.12 (d, $J = 3.3$ Hz, 1H), 6.42 (s, 1H), 6.65 (d, $J = 3.3$ Hz, 1H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 13.7, 28.2, 33,3, 39.0, 51.1, 108.8, 113.9, 118.5, 145.0,$ 150.8, 155.7, 199.3. MS (70 EV, EI, relative intensity): 204 (M$^+$, 96), 189 (11), 176 (24), 148 (100), 120 (54). ESI-HRMS calculated for $C_{13}H_{17}O_2$: 205.1229. Found: 205.1218%.

3.4. 3-(4,5-Dimethyl-furan-2-yl)-cyclohex-2-enone (3d)

IR (neat): $v = 1680, 1640, 1590, 740\ cm^{-1}$. ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 1.96$ (s, 3H), 2.03–2.13 (m, 2H), 2.24 (s, 3H), 2.42 (t, $J = 5.9$ Hz, 2H), 2.57 (t, $J = 6.2$ Hz, 2H), 6.36 (s, 1H), 6.55 (s, 1H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 9.4, 11.4, 22.2, 24.9, 37.2, 116.3, 117.3, 118.9, 147.0, 148.9, 151.2, 198.9$. MS (70 EV, EI, relative intensity): 190 (M$^+$, 100), 162 (60), 134 (43). ESI-HRMS calculated for $C_{12}H_{15}O_2$: 191.1072. Found: 191.1065%.

3.5. 3-(4,5-Dimethyl-furan-2-yl)-5-phenyl-cyclohex-2-enone (3e)

IR (neat): $v = 1695, 1625, 1580, 745\ cm^{-1}$.; ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 1.95$ (s, 3H), 2.25 (s, 3H), 2.62–2.95 (m, 4H), 3.30–3.40 (m, 1H), 6.46 (d, $J = 1.7$ Hz, 1H), 6.55 (s, 1H), 7.25–7.40 (m, 5H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 9.7, 11.7, 33.1, 40.6, 44.3, 116.9, 117.7, 118.8, 126.7, 127.0, 128.7, 143.3, 146.3, 148.9, 151.9, 198.6$. MS (70 EV, EI, relative intensity): 267 [(M+1)$^+$, 100]. ESI-HRMS calculated for $C_{18}H_{19}O_2$: 267.1380. Found: 267.1376%.

3.6. 3-(4,5-Dimethyl-furan-2-yl)- 5,5-dimethyl-cyclohex-2-enone (3f)

IR (neat): $v = 1700, 1640, 1580\ cm^{-1}$. ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 1.08$ (s, 6H), 1.96 (s, 2H), 2.25 (s, 3H), 2.28 (s, 3H), 2.45 (s, 2H), 6.38 (s, 1H), 6.56 (s, 1H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 9.7, 11.7, 28.3, 33.3, 39.1, 51.2, 116.4, 117.5, 118.2, 145.1, 149.5, 151.5, 199.3$. MS (70 EV, EI, relative intensity): 219 [(M+1)$^+$, 100]. ESI-HRMS calculated for $C_{14}H_{19}O_2$: 219.1385. Found: 219.1384%.

3.7. 3-(4,5-Dimethyl-furan-2-yl)-5-methyl-cyclohex-2-enone (3g)

IR (neat): $v = 1680, 1640, 1560\ cm^{-1}$. ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 1.13$ (d, $J = 5.9$ Hz, 3H), 1.96 (s, 3H), 2.10–2.17 (m, 2H), 2.25 (s, 3H), 2.50 (d, $J = 14.8$ Hz, 1H), 2.70 (d, $J = 13.2$ Hz, 1H), 6.37 (s, 1H), 6.56 (s, 1H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 9.7, 11.7, 21.2, 29.7, 33.4, 45.7, 116.4, 117.5, 119.0, 146.5, 149.3, 151.5, 199.5$. MS (70 EV, EI, relative intensity): 205 [(M+1)$^+$, 100]. ESI-HRMS calculated for $C_{13}H_{17}O_2$: 205.1229. Found: 205.1217%.

3.8. 3-(5-Phenyl-furan-2-yl)-cyclohex-2-enone (3h)

IR (neat): $v = 1700, 1690, 1600, 745, 640\ cm^{-1}$. ^{1}H NMR (CDCl$_3$, 200 MHz) $\delta = 2.05$–2.19 (m, 2H), 2.49 (t,

$J = 6.6$ Hz, 2H), 2.69 (t, $J = 5.9$ Hz, 2H),.6.60 (s, 1H), 6.77 (d, $J = 3.6$ Hz, 1H), 6.82 (d, $J = 3.6$ Hz, 1H), 7.38–7.42 (m, 3H), 7.70–7.74 (m, 2H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) $\delta = 22.5, 25.2, 37.5, 107.6, 114.9, 120.7, 123.5, 124.3, 128.5, 128.8, 146.8, 151.4, 156.4, 199.2.$ MS (70 EV, EI, relative intensity): 239 [(M+1)$^+$, 100]. ESI-HRMS calculated for C$_{16}$H$_{15}$O$_2$: 239.1072. Found: 239.1076%.

Acknowledgements

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