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A new method for the synthesis of acyltitanium complexes and their application to copper-mediated acylmetallation of carbon–carbon multiple bonds in aqueous media

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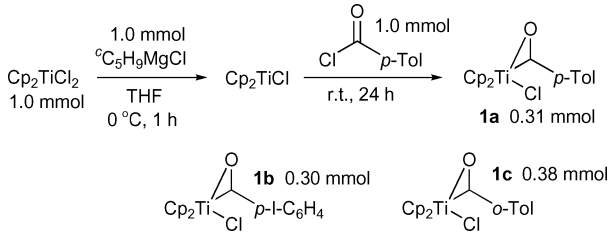
Treatment of α,β-unsaturated carbonyl compounds or methyl propargyl ether with acylchlorobis(cyclopentadienyl)titanium in the presence of triethylamine and a copper salt in aqueous THF resulted in acylation of the carbon–carbon multiple bond, yielding the corresponding 1,4-diketones in good yields.

Acylmetals are important reagents and are widely used in organic synthesis.[1] However, little attention has been paid to the synthesis and reaction of acyltitanium compounds.[2] In this communication we report a facile method for the preparation of acyltitanium compounds and their application to copper-mediated 1,4-addition.

Titanocene dichloride (1.0 mmol) was treated with cyclopentylmagnesium chloride (1.5 mmol) in THF at 0 °C for 1 h to yield Cp_2TiCl (Scheme 1).[3] 4-Methylbenzoyl chloride (*p*-TolC(=O)Cl, 1.0 mmol) was added to the mixture, and the mixture was stirred at 25 °C for 24 h. The resulting precipitate was filtered under air, washed with THF, and dried *in vacuo* to yield 0.31 mmol of acylchlorobis(cyclopentadienyl)titanium **1a**. Possible unavoidable by-products include titanocene dichloride, which was readily removed by the above procedure. This complex was stable under air for more than a few weeks. The complex was identified by elemental analysis, ^1H, ^{13}C NMR, and IR spectroscopy,[4] and showed spectra similar to known η^2-acyl titanocene complexes.[2g] The bromide analogue of **1a** formed a single crystal suitable for X-ray crystallographic analysis, revealing the structure of η^2-acyl complex (Fig. 1). Other complexes such as **1b** and **1c** were prepared in a similar manner. Fortunately, the reaction tolerated a $C(sp^2)$–I bond.



Scheme 1 Synthesis of acyltitanium complexes.

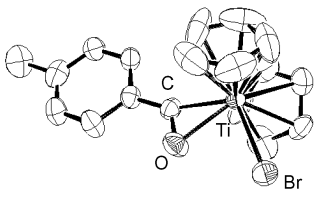
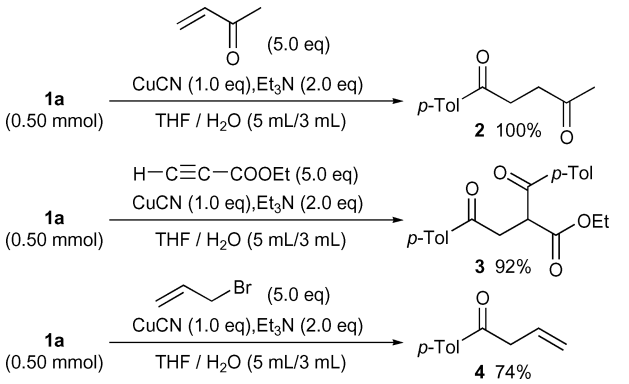


Fig. 1 ORTEP diagram of the bromide analogue of **1a**.[5] Hydrogen atoms are omitted for clarity.

We turned our attention to the application of the acyltitanium complexes to organic synthesis. Gratifyingly, we found that treatment of methyl vinyl ketone (2.5 mmol) with **1a** (0.50 mmol) in the presence of triethylamine (1.0 mmol) and copper(I) cyanide (0.50 mmol) in aqueous THF (THF–water 5 : 3) provided the corresponding 1,4-diketone **2** quantitatively, based on **1a** (Scheme 2). It is worth noting that the absence of water, base, or copper salt resulted in the formation of complex mixtures. The reaction with ethyl propiolate furnished tricarbonyl compound **3** in excellent yield. Addition to ethyl 2-butynoate did not produce any of the expected products. Allylic substitution of allyl bromide proceeded smoothly to give allyl ketone **4**.



Scheme 2 Copper-mediated 1,4-addition and allylic substitution with acyltitanium in aqueous media.

Interestingly, double acylation occurred in the reaction of methyl propargyl ether (Table 1, entry 1) as well as propiolate, although the reaction suffered from a lower yield. To improve the yield of **5a**, screening of reaction conditions was performed. Other copper(I) salts did not result in any dramatic improvement (entries 2–6). No **5a** was obtained under catalysis by copper(II) salts (entries 7 and 8). Intriguingly, both CuO and Cu_2O mediated the double acylation (entries 9 and 10). We finally found that metallic copper powder purchased from Aldrich (99.999% purity) enhanced the efficiency of the reaction (entry 11). Copper powders from other companies such as Wako Pure Chemical were also effective, although the yields were lower. Triethylamine proved to be the base of choice after intensive screening (entries 16–25). The amounts of water, triethylamine, and copper were varied until no further improvement could be obtained.

Under the optimized conditions (entry 11 in Table 1), the double acylation of various alkynes were surveyed (Table 2). Propargyl alcohol underwent acylation to provide **5b** in 42% yield (entry 1), whereas its silyl ether resisted acylation (entry 2). Aliphatic as well as aromatic acetylenes reacted to yield the corresponding 1,4-diketones (entries 3–5). Ethyl ethynyl ether

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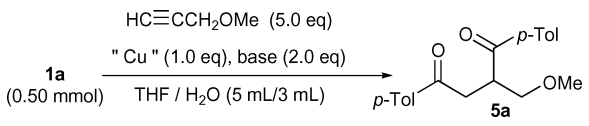
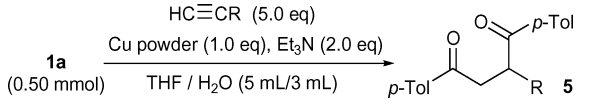
Table 1 Double acylation of methyl propargyl ether



Entry	"Cu"	Base	Yield of **5a** (%)
1	CuCN	Et_3N	56
2	CuI	Et_3N	42
3	CuBr	Et_3N	52
4	CuCl	Et_3N	54
5	CuOAc	Et_3N	56
6	CuSPh	Et_3N	57
7	$Cu(OAc)_2$	Et_3N	0
8	$Cu(OTf)_2$	Et_3N	0
9	CuO	Et_3N	57
10	CuO_2	Et_3N	39
11	Cu (Aldrich)[a]	Et_3N	73
12	Cu (Aldrich, nanosize)[b]	Et_3N	51
13	Cu (Wako)[c]	Et_3N	68
14	Cu (Kanto)[d]	Et_3N	66
15	Cu (Merck)[e]	Et_3N	58
16	Cu (Aldrich)	Et_2NH	66
17	Cu (Aldrich)	$PrNH_2$	18
18	Cu (Aldrich)	NH_3	6
19	Cu (Aldrich)	Pyridine	0
20	Cu (Aldrich)	Imidazole	0
21	Cu (Aldrich)	DBU	14
22	Cu (Aldrich)	1-Methylpiperidine	49
23	Cu (Aldrich)	$^iPr_2NEt$	60
24	Cu (Aldrich)	DMAP	31
25	Cu (Aldrich)	K_2CO_3	39

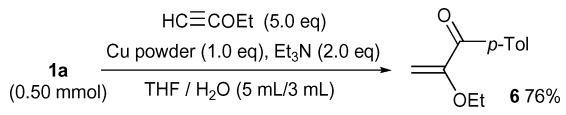
[a] Cat. no. 203122-10G, 99.999%. [b] Cat. no. 48392-3, nanosize activated powder, >99.9% [c] Cat. no. 031-03992, >99.85%. [d] Cat. no. 07439-33, >99.5%. [e] Cat. no. 1.02703.0250, >99.7%.

Table 2 Double acylation of alkynes



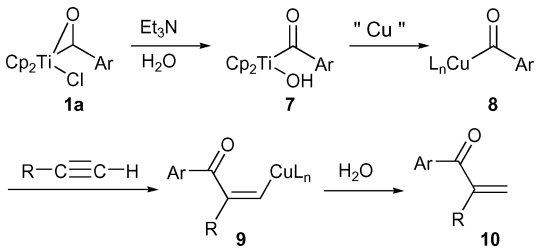
Entry	R	Product	Yield (%)
1	CH_2OH	**5b**	42
2	$CH_2OSi^tBuMe_2$	**5c**	trace
3	Ph	**5d**	28
4	p-$MeOC_6H_4$	**5e**	37
5	$^nC_6H_{13}$	**5f**	43

underwent monoacylation to afford **6** regioselectively in good yield (Scheme 3).



Scheme 3 Addition to ethyl ethynyl ether.

The exact mechanism of the acylation reaction, especially the roles of water and triethylamine, is not clear at this stage. As outlined in Scheme 4, a combination of triethylamine and water could transform **1a** to a putative η^1-acyltitanium complex such as



Scheme 4 A possible mechanism for the reaction of unactivated alkynes.

7. The η^1-complex would transfer the acyl moiety more readily to copper. The resulting copper reagent **8** would seem to be able to resist hydrolysis, and effects acylcupration to yield the vinylic copper compound **9**, which would be readily hydrolyzed.[6] Further addition of an acyl moiety would afford doubly acylated products.

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4 Spectral data for **1a**: IR 1566 cm^{-1}; ^1H NMR (δ/ppm, $CDCl_3$) 2.54 (s, 3H), 5.84 (s, 10H), 7.49 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H); ^{13}C NMR (δ/ppm, $CDCl_3$) 22.44, 110.40, 130.17, 130.43, 130.78, 147.16, 282.23.

5 Crystal data for the bromide analogue of **1a**: formula, $C_{18}H_{17}BrOTi$ (FW = 377.13), orange blocks, triclinic, $P\bar{1}$, a = 7.7237(7) Å, b = 9.8885(9) Å, c = 11.0929(10) Å, α = 81.444(2)°, β = 70.937(2)°, γ = 89.529(2)°, V = 791.12(12) Å^3, Z = 2, T = 293 K; no. of reflections measured: 4848, observed: 3431 ($I > 2.00\sigma(I)$), $R1$ = 0.0335 ($I > 2.00\sigma(I)$), $wR2$ = 0.0892 ($I > 2.00\sigma(I)$), $R1$ = 0.0417 (all data), $wR2$ = 0.0926 (all data). CCDC reference number 265208. See http://www.rsc.org/suppdata/ob/b5/b503117f/ for crystallographic data in CIF or other electronic format.

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