Room temperature palladium catalysed coupling of acyl chlorides with terminal alkynes†

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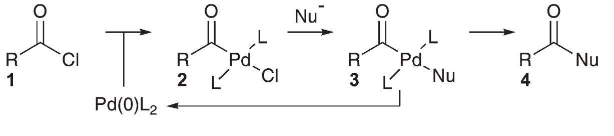
Conditions are reported for the facile, high-yielding coupling of acyl chlorides with terminal alkynes in a reaction involving palladium and copper iodide; the reaction is tolerant of a wide variety of acyl chlorides and terminal alkynes and provides a convenient one-pot route to acetylenic ketones.

Acetylenic ketones are useful precursors for organic synthesis, especially as precursors during the synthesis of saturated polycyclic[1] and heterocyclic[2] compounds. However their synthesis is not straightforward because the addition of acetylenic nucleophiles to acyl chlorides or acid anhydrides can be accompanied by unwanted addition to the products, forming bis-acetylenic tertiary alcohols.[3] An alternative route involving addition of acetylenic Grignard reagents, for example, to aldehydes can be low-yielding and requires a subsequent oxidation reaction.[2,4]

We reasoned that because acyl chlorides are known to oxidatively add to Pd(0) species, forming an acyl Pd(II) intermediate,[5] it should be possible to intercept this species with a suitable nucleophile (Scheme 1). For example, others have reported the use of boronic acids as nucleophiles in similar processes.[6] In the classical Sonogashira reaction, terminal alkynes are activated as nucleophiles under basic conditions using a CuI co-catalyst. The precise identity of the Pd catalyst active in these reactions is not known, but could involve discrete Pd(0)L_2 species or Pd nanoclusters as has recently been demonstrated for Heck reactions.[7] Sonogashira also reported that terminal acetylenes would react with acid chlorides when catalysed by Pd(0) and CuI, but the reactions were limited by unwanted reaction between the acid chlorides and the Et_3N solvent, reducing yields.[8] More recently Najera and co-workers have reported a similar reaction, but at high temperature and in the absence of Cu, giving moderate isolated yields of products.[9] We now report a simple procedure which operates at RT giving high isolated yields of products.



Scheme 1 Catalytic cycle for the Pd(0) catalysed coupling of acid chlorides.

In order to reduce the chance of reaction between the acid chloride component and the base, we reduced the base concentration and used 1.25 eq. of NEt_3 in THF rather than neat base as the solvent. Using these conditions with $PdCl_2(PPh_3)_2$ (0.9 mol%) and CuI (3.0 mol%) in dry THF at RT, the reaction between phenylacetylene (1.0 eq.) and benzoyl chloride (1.5 eq.) was complete by TLC analysis within 10 minutes (Table 1) (See ESI for experimental procedures).† The product **5** was isolated in 96% yield after purification.

The reaction is tolerant of a wide range of functional groups on the acetylene (Table 1), in particular alkyl, ester, silyl, silyloxy and protected amino groups are compatible, all giving isolated purified products in high yields. We also tested a range of aromatic acyl chlorides (Table 2, entries 1–4. Once again, good to high yields of purified products were obtained rapidly. *p*-Nitrobenzoyl chloride yielded the highly crystalline **14** (Fig. 1).‡

In the case of the *p*-bromobenzoyl chloride, the expected product **15** was obtained, and no reaction of the bromide was observed. However, in the case of the *p*-iodobenzoyl chloride, the acyl chloride and iodo groups appeared to be equally reactive, and in the presence of two equivalents of acetylene, the bis-acetylene **16** was formed in high yield.

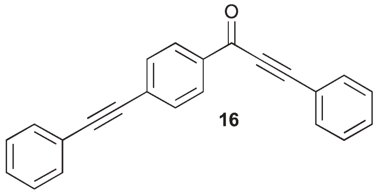


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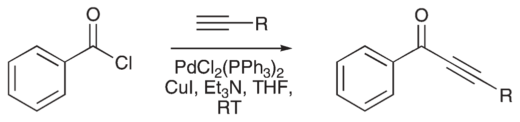
Table 1 Coupling reactions of benzoyl chloride



Entry	R	Product	Yield (%)[a]
1	C_6H_5	**5**	96
2	$(CH_2)_2CO_2Me$	**6**	89
3	$(CH_2)_2CO_2{}^tBu$	**7**	84
4	$(CH_2)_3CH_3$	**8**	88
5	$Si(CH_3)_2{}^tBu$	**9**	96
6	$CH_2OSi(CH_3)_2{}^tBu$	**10**	94
7	$CH_2NH(BOC)$[b]	**11**	91
8	CH_2NHAc	**12**	70

[a] Isolated purified yield. [b] 1 h reaction.

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† Electronic Supplementary Information (ESI) available: experimental procedures, characterisation for compounds **5**–**28** and crystal structure data for **14**. See http://www.rsc.org/suppdata/cc/b4/b414826f/
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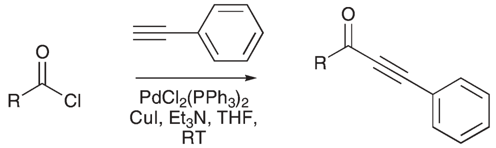
Table 2 Coupling reactions of phenylacetylene



Entry	R	Product	Yield (%)^a
1	pMeOC$_6$H$_4$	**13**	98
2	pO$_2$NC$_6$H$_4$	**14**	50^b
3	pBrC$_6$H$_4$	**15**	89
4	pIC$_6$H$_4$	**16**	66^e
5	^{t}Bu^c	**17**	86
6	C$_6$H$_{11}$	**18**	96
7	(CH$_3$)$_2$CH	**19**	97
8	CH$_3$(CH$_2$)$_2$	**21/22**	43^d

[a] Isolated purified yield. [b] Recrystallised yield. [c] overnight reaction. [d] using DIPEA as the base. [e] using two equivalents of acetylene.

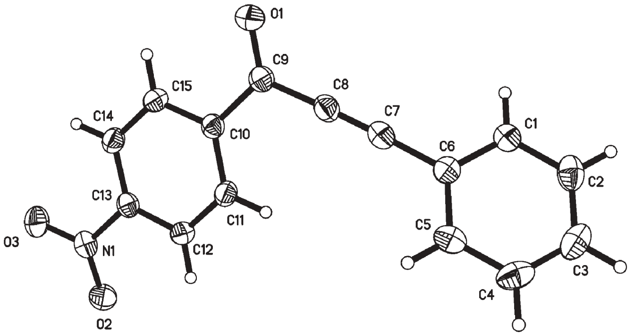
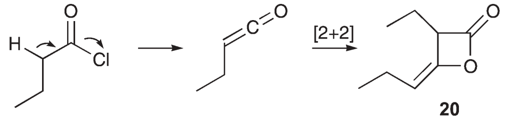


Fig. 1 X-ray crystal structure of p-nitrophenyl ketone **14**.‡



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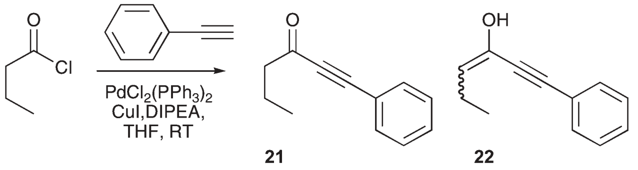
Scheme 2 Reaction of linear aliphatic acid chlorides.

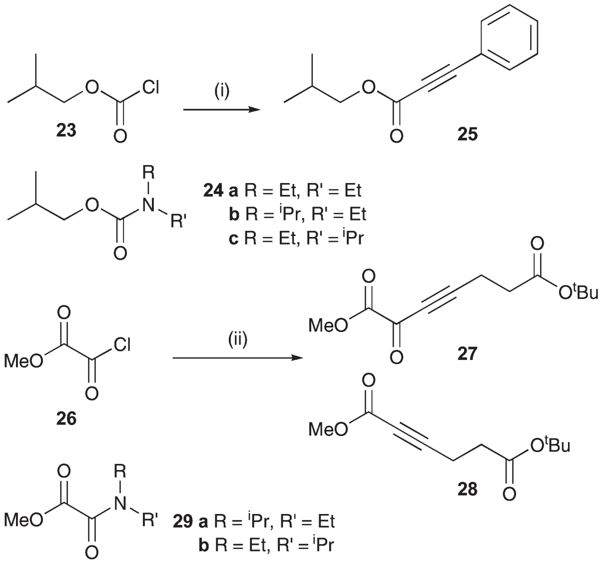
Pivaloyl chloride, cyclohexylcarboxylic acid chloride and 2-methylpropionyl chloride also reacted smoothly to give high yields of the acetylenic ketones **17**, **18** and **19**. However, in the case of butyryl chloride, oxetane **20** was obtained in 46% isolated yield (Scheme 2). This presumably results from [2 + 2] cycloaddition reactions of ketenes. Such compounds are known to arise from the direct reaction of NEt$_3$ with aliphatic acyl chlorides,[10] and in control reactions, using our standard reaction conditions but lacking the Pd catalyst, we observed the formation of **20** by TLC and ^{1}H NMR.

However, in the presence of the more hindered base diisopropylethylamine (DIPEA, Hunig's base) the reaction of butyryl chloride was more productive, giving a mixture of the desired product **21**, together with both isomers of the corresponding enol **22** (Scheme 3) in 43% combined yield.



21 **22**

Scheme 3 Reaction of linear aliphatic acyl chlorides.



Scheme 4 Low-yielding coupling reactions. *Reagents and conditions*: (i) HCCPh, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N or DIPEA, THF, RT, 8%; (ii) HCC(CH$_2$)$_2$CO$_2$^{t}Bu, PdCl$_2$(PPh$_3$)$_2$, CuI, DIPEA, THF, RT, 4%.

In an effort to broaden the range of potential acyl partners, we used isobutyryl chloroformate **23** in an attempt to synthesise acetylenic esters (Scheme 4). In the presence of Et$_3$N, the only product was the corresponding *O*-isobutyryl-*N*,*N*-diethylcarbamate **24a** formed by attack of the base on the carbonyl. In the presence of DIPEA the desired product **25** was formed but in 8% yield: the balance of the reaction was the corresponding carbamate rotamers **24b** and **c**. Similar results were obtained when using methyloxalylchloride **26**. Using DIPEA as the base, this reacted to give a mixture of the desired product **27** (4%), a decarbonylated product **28** (4%) and the balance of the reaction as amide rotamers **29a** and **b**. These reactions, however, did indicate the intermediacy of an acyl-palladium species. Oxalyl-palladium species are known to easily decarbonylate,[11] and decarbonylation and interception by the amine[12] clearly compete with transfer of the acetylene in these cases.

Thus the reaction of terminal acetylenes with acid chlorides under room temperature Pd(0) catalysed conditions is a rapid and high-yielding method for the construction of synthetically useful acetylenic ketones. The product yields are significantly improved over previous reports[8] and a wide variety of substituents are tolerated on the acetylene. Aromatic and α-branched aliphatic acid chlorides bearing a variety of substituents can be used. Linear aliphatic acid chlorides also react in the presence of DIPEA. The reaction conditions are mild enough that aromatic bromo-substituents, which could be used for subsequent organo-metallic coupling reactions, do not react but aromatic iodides are reactive under these conditions.

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Notes and references

‡ CCDC 252032. See http://www.rsc.org/suppdata/cc/b4/b414826f/ for crystallographic data in .cif or other electronic format. Crystal data for compound **14**. $C_{15}H_9NO_3$, M = 251.23, monoclinic, *a* = 7.6488(6), *b* = 7.1371(6), *c* = 10.9816(9) û, *β* = 97.617(2)ō, *U* = 594.20(8) û^3, *T* =173(2) K, space group $P2_1$ (no. 4), *Z* = 2, *ôç*(Mo–Kα) = 0.099 mm^{-1}, 3914 reflections measured, 2516 unique (R_{int} = 0.0185) which were used in all calculations. The final R_1 and wR_2 were 0.0310 and 0.0796 (I>2σI).

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12 The presence of $PdCl_2(PPh_3)_2$ in these reactions appeared to increase the rate of formation, and the yield, of amide and carbamate products.