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Unprecedented carbon dioxide effect on a Pd-catalysed oxidative carbonylation reaction: a new synthesis of pyrrole-2-acetic esters

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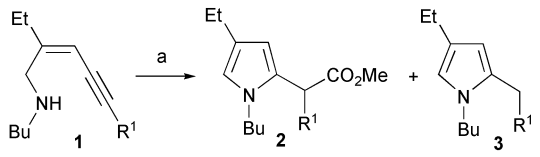
It has been found that carbon dioxide effectively promotes the Pd-catalysed oxidative cyclisation–alkoxycarbonylation of (*Z*)-(2-en-4-ynyl)amines 1 leading to pyrrol-2-acetic esters 2.

We recently described a new synthesis of furan-2-acetic esters by PdI_2/KI-catalysed oxidative cyclisation–alkoxycarbonylation of (*Z*)-2-en-4-yn-1-ols.[1] When we applied this methodology to (*Z*)-(2-en-4-ynyl)amines **1**, however, the desired pyrrole-2-acetic esters **2** were consistently obtained in low yield, even after optimisation of the reaction conditions. For example, carbonylation of (*Z*)-butyl(2-ethylnon-2-en-4-ynyl)-amine **1a** under 40 atm of a 3:1 mixture of carbon monoxide and air in MeOH at 70 °C for 5 h (substrate/KI/PdI_2 molar ratio = 100:200:1, substrate concentration = 0.05 mmol mL^{-1} MeOH) afforded a mixture of methyl 2-(1-butyl-4-ethyl-1*H*-pyrrol-2-yl)hexanoate **2a** (45% GLC yield, 40% isolated) and 1-butyl-4-ethyl-2-pentyl-1*H*-pyrrole **3a** (deriving from a competitive cycloisomerization process,[2] 9% GLC yield) at total substrate conversion [eqn. (1)].



(1)

a R^1 = Bu
b R^1 = TMS

a R^1 = Bu, 45%
b R^1 = H, 36%

a R^1 = Bu, 9%
b R^1 = H, 4%

a PdI_2 : KI : **1** molar ratio = 1:200:100, CO (30 atm), air (10 atm), solvent MeOH, substrate concn = 0.05 mmol/mL MeOH, 70 °C, 5 h

The striking difference in the behaviour of enynols and enynamines can be ascribed to the basicity of the latter.[3] The alkoxycarbonylation process occurs with reduction of PdI_2 to Pd(0) and formation of 2 mol of HI. Pd(0) is then reoxidised to the catalytically active species PdI_2 by I_2, formed by oxidation of HI with oxygen[4] (Scheme 1; anionic iodide ligands are omitted for simplicity). The latter process is very fast in the case of (*Z*)-2-en-4-yn-1-ols or in general with non-basic substrates. However, substrates that are basic enough to be protonated by HI, such as enynamines, can efficiently inhibit the reoxidation of Pd(0) and therefore hinder the overall oxidative carbonylation process. When this occurs, the substrate may undergo undesired side-reactions such as oligomerisation and/or oxidative degradation.

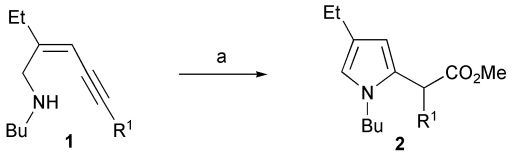
One way for accelerating the Pd(0) reoxidation process when inhibited by a basic substrate consists of the use of a large excess of oxygen (which apparently favours the oxidation of HI to iodine).[3b] A large excess of oxygen for the carbonylation of enynamines, however, could not be used owing to the tendency of the pyrrole ring to undergo oxidation reactions.[5] It was therefore necessary to solve the problem in a different manner. A reactant able to reversibly bind the amino group [thus 'freeing' the HI necessary for the reoxidation of Pd(0)] without hampering the cyclisation–alkoxycarbonylation process was needed. We have found that carbon dioxide effectively fulfils these requirements, through the formation of a carbamate species. The nitrogen in the carbamate, while much less basic than in the substrate, may still act as nucleophile, since CO_2 can be eliminated during the cyclisation process (Scheme 2).

In fact, by reacting **1a** under the above-mentioned conditions but with the addition of 50 atm of CO_2, **2a** was obtained in 70% GLC yield (62% isolated) at total substrate conversion, without any formation of **3a** [eqn. (2)].†

In order to support our hypothesis regarding the effect exerted by CO_2, we synthesized allyl carbamate **4** and let it react under the above-mentioned conditions but in the absence of CO_2. Palladium-promoted cleavage of the allyl group of **4** was expected to afford exactly the same carbamate intermediate formed in the CO_2-assisted carbonylation of **1a** (Scheme 3).‡

Indeed, by reacting **4** in the absence of CO_2 and under 6 atm of a 5:1 mixture of CO and air, after 48 h **2a** was obtained in 46% GLC yield at total substrate conversion, with complete absence of pyrrole **3a**.§ In agreement with the mechanism shown in Scheme 3, the allyl moiety of **4** was recovered as methyl but-3-enoate.

Under the optimised conditions found for **1a**, other (*Z*)-(2-en-4-ynyl)amines **1** were efficiently carbonylated to selectively afford the corresponding pyrrole-2-acetic esters **2** in good yields. For example, methyl (1-butyl-4-ethyl-1*H*-pyrrol-2-yl)-acetate **2b** was obtained in 72% GLC yield (65% isolated) from the reaction of (*Z*)-butyl[2-ethyl-5-(trimethylsilanyl)pent-2-en-4-ynyl]amine **1b** at total substrate conversion [eqn. (2)].†

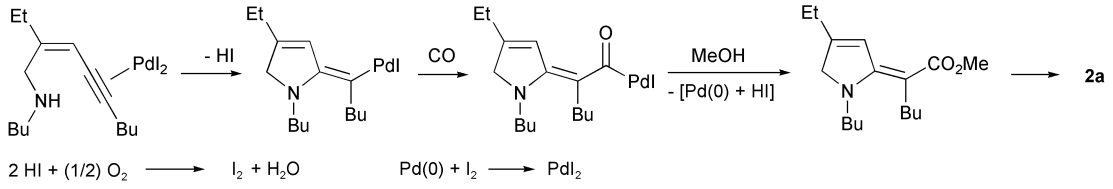


(2)

a R^1 = Bu
b R^1=TMS

a R^1 = Bu, 70%
b R^1= H, 72%

a PdI_2 : KI : **1** molar ratio = 1:200:100, CO (30 atm), air (10 atm), CO_2 (50 atm), substrate concn = 0.05 mmol/mL MeOH, 70 °C, 5 h



Scheme 1 Mechanism of the PdI_2/KI-catalysed oxidative carbonylation of **1a** to give **2a**. Anionic iodide ligands are omitted for clarity.

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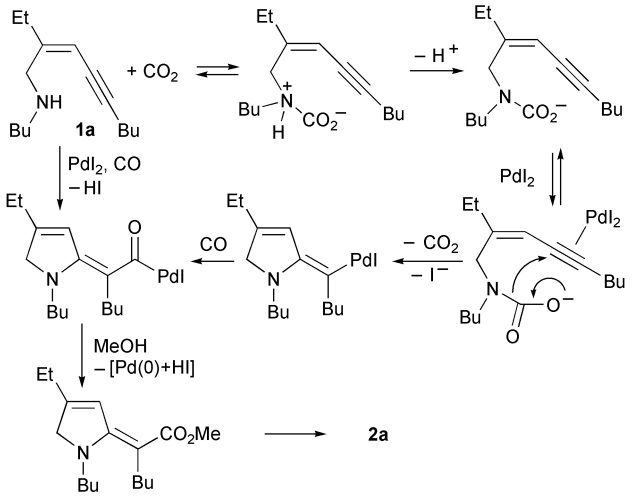
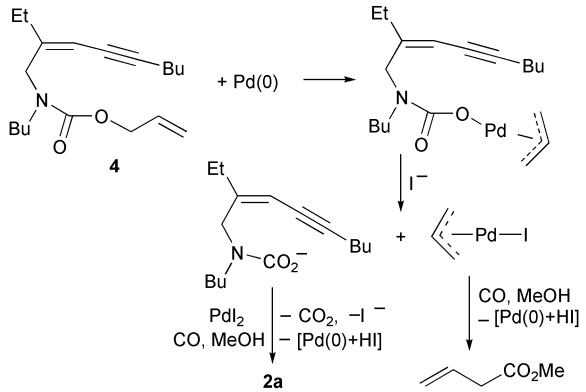


Scheme 2 Carbon dioxide effect on the PdI_2/KI-catalysed oxidative cyclisation–alkoxycarbonylation of **1a** to methyl pyrrol-2-acetate **2a**.



Scheme 3 Cleavage and carbonylation of **4** leading to **2a**.

This result should be compared with that obtained in the same reaction carried out in the absence of CO_2, which led to a mixture of **2b** and 1-butyl-4-ethyl-2-methyl-1*H*-pyrrole **3b** in 36% and 4% GLC yield, respectively [eqn. (1)]. As we already observed in the oxidative carbonylation of (*Z*)-(5-trimethylsilanyl)-2-en-4-yn-1-ols,[1] the trimethylsilanyl group was lost in the course of the process, thus allowing the synthesis of α-unsubstituted pyrrolacetates starting directly from (*Z*)-(5-trimethylsilanyl-2-en-4-ynyl)amines.

The reaction reported here represents the first example in which carbon dioxide is shown to act as a *promoter* in an oxidative carbonylation process.[6] From a synthetic point of view, this is the first example of direct synthesis of pyrrole-2-acetic esters by carbonylation of acyclic precursors. Pyrrole-2-acetic derivatives are a very interesting class of compounds, which are known to posses a marked pharmacological activity.[7] Moreover, they have also found application as synthetic intermediates in a variety of useful transformations.[8] The present methodology offers a convenient alternative to the so far known methodologies[9] for the synthesis of these molecules, starting from readily available[2] starting materials.

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Progetto d'Interesse Nazionale PIN MM03027791_005).

Notes and references

† Starting (*Z*)-(2-en-4-ynyl)amines **1** were prepared as described in reference 2. Representative experimental procedure for the synthesis of **2**: a 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (4.0 mg, 0.011 mmol), KI (365 mg, 2.20 mmol) and **1** (1.1 mmol) dissolved in MeOH (22 mL). The autoclave was pressurized with stirring at room temperature with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 70 °C with stirring for 5 h. After cooling, the autoclave was degassed and solvent removed by rotary evaporation. Crude products were easily purified by column chromatography on silica gel using hexane/AcOEt from 99 : 1 to 95 : 5 as eluent. *Characterization data* for **2a** (190 mg, 62% yield; pale yellow oil): IR (film): ν = 2957, 1743, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H), 1.16 (t, *J* = 7.6 Hz, 3 H), 1.23–1.41 (m, 6 H), 1.60–1.71 (m, 2 H), 1.71–1.84 (m, 1 H); 1.98–2.13 (m, 1 H), 2.41–2.50 (m, 2 H), 3.54 (dd, *J* = 8.8, 6.8 Hz, 1 H), 3.66 (s, 3 H), 3.65–3.90 (m, 2 H), 5.91 (d, *J* = 2.0 Hz, 1 H), 6.35–6.37 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.9, 14.9, 20.1, 20.2, 22.6, 30.0, 32.5, 33.8, 43.3, 46.2, 51.9, 106.2, 117.4, 125.2, 129.5, 173.9; MS (EI, 70 eV): *m*/*z* (%): 279 (13) [M^+], 220 (100). For **2b** (160 mg, 65%; pale yellow oil): IR (film) ν = 2959, 1741, 1461 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3 H), 1.16 (t, *J* = 7.5 Hz, 3 H), 1.27–1.41 (m, 2 H), 1.61–1.73 (m, 2 H), 2.41–2.50 (m, 2 H), 3.58 (s, 2 H), 3.69 (s, 3 H), 3.75 (t, *J* = 7.3 Hz, 2 H), 5.89 (d, *J* = 2.0 Hz, 1 H), 6.40–6.42 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 15.1, 20.09, 20.12, 32.6, 33.5, 46.4, 52.0, 108.4, 117.8, 123.9, 125.2, 171.2; MS (EI, 70 eV): *m*/*z* (%): 223 (35) [M^+], 164 (100). Elemental analyses were satisfactory.

‡ In Scheme 3, the cleavage is shown to occur through oxidative addition to a Pd(0) species formed by reduction of PdI_2 under the reaction conditions. However, the possibility of formation of a Pd(IV) intermediate by oxidative addition to PdI_2 cannot be ruled out.

§ The reaction was slower under 30 atm of CO and 10 atm of air probably due to the competition between CO and the substrate for coordination to palladium. A longer reaction time with respect to the analogous carbonylation of **1a** carried out in the presence of CO_2 was needed owing to the kinetics of cleavage of the allyl moiety.

1 B. Gabriele, G. Salerno, F. De Pascali, M. Costa and G. P. Chiusoli, *J. Org. Chem.*, 1999, **64**, 7693.

2 B. Gabriele, G. Salerno, A. Fazio and M. R. Bossio, *Tetrahedron Lett.*, 2001, **42**, 1339.

3 We have already shown that the presence of an amino group in the substrate has an adverse effect on catalysis in PdI_2/KI-catalysed oxidative alkoxycarbonylation reactions: (*a*) A. Bonardi, M. Costa, B. Gabriele, G. Salerno and G. P. Chiusoli, *Tetrahedron Lett.*, 1995, **36**, 7495; (*b*) B. Gabriele, G. Salerno, D. Brindisi, M. Costa and G. P. Chiusoli, *Org. Lett.*, 2000, **2**, 625.

4 B. Gabriele, M. Costa, G. Salerno and G. P. Chiusoli, *J. Chem. Soc., Perkin Trans. 1*, 1994, 83.

5 R. A. Jones, in *Comprehensive Heterocyclic Chemistry, Vol. 4*, eds. A. R. Katritzky, C. W. Rees, C. W. Bird and G. W. H. Cheeseman, Pergamon, Oxford, 1984, pp. 246–254.

6 We have recently shown that it is possible to sequentially insert CO and CO_2 into propynylamines to give oxazolidinone derivatives, but in this reaction CO_2 was incorporated in the reaction product: A. Bacchi, G. P. Chiusoli, M. Costa, B. Gabriele, C. Righi and G. Salerno, *Chem. Commun.*, 1997, 1209; G. P. Chiusoli, M. Costa, B. Gabriele and G. Salerno, *J. Mol. Catal. A: Chem.*, 1999, **143**, 297.

7 For some recent examples, see: C. Dendrinousomara, G. Tsotsou, L. V. Ekateriniadou, A. H. Kortsaris, C. P. Reptopoulou, A. Terzis, D. A. Kyriakidis and D. P. Kessissoglou, *J. Inorg. Biochem.*, 1998, **71**, 171; M. Lehr, *J. Med. Chem.*, 1997, **40**, 3381; M. Lehr, *Eur. J. Med. Chem. Chim. Ther.*, 1997, **32**, 805.

8 For some recent examples, see: P. Langer, J. Wuckelt and M. Doring, *J. Org. Chem.*, 2000, **65**, 729; C. Peschko and W. Steglich, *Tetrahedron Lett.*, 2000, **41**, 9477; A. Ohta, D. Sawamoto, K. P. Jayasundera, H. Kinoshita and K. Inomata, *Chem. Lett.*, 2000, 492; T. L. Gilchrist, A. Lemos and C. J. Ottaway, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3005; D. A. Lee and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1215.

9 For some recent examples, see: R. Grigg and V. Savic, *Chem. Commun.*, 2000, 873; O. A Attanasi, L. De Crescentini, P. Filippone and F. Mantellini, *Synlett.*, 2000, 955; M. Johannsen, *Chem. Commun.*, 1999, 2233; J. H. Byers, J. E. Campbell, F. H. Knapp and J. G. Thissel, *Tetrahedron Lett.*, 1999, **40**, 2677; H.-J. Grumbach, B. Merla and N. Risch, *Synthesis*, 1999, 1027; H. M. C. Ferraz, F. L. C. Pereira, F. S. Leite, M. R. S. Marta and M. E. Payret-Arrua, *Tetrahedron*, 1999, **55**, 10915.