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Tetrahedron Letters 45 (2004) 8621–8623

Tetrahedron Letters

A solid-phase iridium-based *ortho*-exchange catalyst for the one-step labelling of aromatic substrates with deuterium

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Received 9 August 2004; revised 22 September 2004; accepted 27 September 2004

Abstract—A wide range of aromatic compounds containing suitable directing groups can be labelled efficiently with deuterium using isotopic exchange catalysed by an easily prepared polystyrene based *ortho*-exchange catalyst. The labelling reactions can be carried out efficiently at ambient temperature by simple stirring of the substrate and catalyst under a deuterium atmosphere for a few hours. Isolation consists of a simple filtration and evaporation of the solvent. Deuterium is incorporated with *ortho*-regiospecificity.

The preparation of labelled organic compounds is often essential in the chemical, biological and environmental sciences. Of the numerous methodologies that have been developed for the ^{2}H- and ^{3}H-labelling of organic substrates, one of the most versatile is *ortho*-directed hydrogen isotope exchange. The isotope for such *ortho*-exchange procedures may derive from isotopic water or isotopic hydrogen gas. The former is often the isotope donor of choice for high deuterium abundance labelling whilst the latter is particularly convenient for labelling with tritium at high abundance. In this case the Crabtree catalyst,[1] or variants thereof, are utilised and considerable work has been reported aimed at understanding the factors controlling the labelling process in these cases.[2] Most of this work has utilised the deuterium isotope.

The above approach has two clear drawbacks. First, the catalysts have little activity outside a limited range of nonpolar solvents. Several attempts to address this limitation have been made. Thus, a detailed study of ionic liquid solvents reported recently identified several in which the catalysts retained activity,[3] whilst we recently reported that similar catalysts based upon cycloocta-1,5-dienyliridium(I) acetylacetonate allow the deuteration of some substrate classes in even polar solvents.[4] The second, serious, drawback is the separation of the labelled product from the catalyst and catalyst derived products, both of which may also be labelled.[5] A traditional approach to simplifying such separations is to 'hetereogenise' the catalyst such that separation is reduced to a simple filtration. A dendrimeric catalyst that is separable by nanofiltration has been described for this purpose.[2b] We now report that an efficient solid-phase *ortho*-exchange catalyst, based on easily separable polystyrene beads, can be prepared in a single step[6] from commercially available starting materials.

Simple treatment of commercially available polystyrene-bound triphenylphosphine[7] with (cycloocta-1,5-diene)-(tricyclohexylphosphine)(pyridine)iridium(I) hexafluorophosphate (Crabtree's catalyst) in dichloromethane yields a red polymeric catalyst, **1**, with high activity for *ortho*-directed isotopic exchange.

The activity of **1** was compared with that of three common homogeneous catalysts by studying the deuteration of a selection of organic substrates possessing known *ortho*-directing groups. To allow good discrimination of

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Keywords: *ortho*-Labelling; Cycloocta-1,5-dienyliridium(I); Deuteration; CH-activation; Isotope exchange; Solid-phase catalyst; Polystyrene; Triphenylphosphine; Crabtree's catalyst.

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doi:10.1016/j.tetlet.2004.09.159

Table 1.

Substrate	Catalyst	Labelling (location)
N,*N*-Dimethylbenzamide	Polymer catalyst **1**	27%D[*]
	Crabtree catalyst	56%D
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	0%D
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	0%D
7,8-Benzoquinoline	Polymer catalyst **1**	14%D (at position 10)
	Crabtree catalyst	7%D (at position 10)
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	0%D
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	0%D
Benzophenone	Polymer catalyst **1**	69%D *ortho*
	Crabtree catalyst	49%D *ortho*
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	81%D *ortho*
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	86%D *ortho*
4-Nitroacetophenone	Polymer catalyst **1**	45%D (*ortho* to C=O)
	Crabtree catalyst	32%D (*ortho* to C=O)
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	81%D (*ortho* to C=O)
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	86%D (*ortho* to C=O)
3-Methylacetophenone	Polymer catalyst **1**	79%D *ortho* D
	Crabtree catalyst	81%D *ortho* D
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	31%D *ortho* D
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	32%D *ortho* D
2-Phenylpyridine	Polymer catalyst **1**	17%D (phenyl-*ortho*-D)
	Crabtree catalyst	21%D (phenyl-*ortho*-D
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	45%D (phenyl-*ortho*-D)
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	50%D (phenyl-*ortho*-D)
Benzanilide	Polymer catalyst **1**	73%D *ortho* to amide, 36%D to anilide
	Crabtree catalyst	68%D *ortho* to amide, 18%D to anilide
	$\mathrm{CODIr(PPh_3)_2{\cdot}BF_4}$	79%D *ortho* to amide, 0%D to anilide
	$\mathrm{CODIr(PPh_3)_2{\cdot}PF_6}$	77%D *ortho* to amide, 0%D to anilide

Conditions: The substrate (0.05 mmol), catalyst (0.001 mmol of the homogeneous catalysts or 1.6 mg of **1**) were stirred in dichloromethane (1 ml) at room temperature for 1 h under D_2 gas (9 ml).

[*] ^{2}H NMR also showed ca. 20% of the incorporated deuterium was located in the N-Me groups.

the catalyst activities the reactions were halted at 1 h, a time at which only the most active exchange sites in the substrates were approaching equilibrium. The results are shown in Table 1. The regiochemistry of labelling was analysed by ^{1}H NMR and, in the case of the polymer catalyst, also by ^{2}H NMR. The catalyst proved effective in labelling all the substrates and the recoveries were good.

To demonstrate the utility of the catalyst in labelling substrates at high atom % abundance an example is given of the preparation of tetradeuterobenzanilide.[8]

Prior to the above studies, catalyst batches were prepared at differing molar ratios of Crabtree's catalyst to the polymer triphenylphosphine groups and the batches were found to have good activity for molar ratios between 1:2 and 3:2 with a ratio ca. 1:1 yielding the most active catalyst. Subsequently all batches of **1** were prepared at this latter ratio.

Since the formation of an iridium dihydride species is considered to be a key step in the catalytic labelling reaction, the amount of active iridium sites on the catalyst was determined by quantification of the cyclooctane released upon exposure to hydrogen. By this procedure, the catalyst had 0.6 mmol of COD, and hence of iridium, per gram of polymer.

The labelling efficiency of **1** in different solvents was studied using benzanilide as the substrate and showed the same limitation as the known homogeneous alternatives. The activity took the following rank order: dichloromethane > diethyl ether > chloroform = toluene > ethyl acetate. Activity was of a very low order in THF, acetone, methanol and DMA.

Studies of the release of the tricyclohexylphosphine and pyridine upon formation of **1** together with the corresponding homogeneous reaction between Crabtree's catalyst and triphenylphosphine suggest that **1** has a structure similar to a catalyst previously described[9] for use in olefin isomerisation. Indeed, when **1** is used to effect the isomerisation of allylbenzene to *trans*-β-methylstyrene it is also found to be very active.

In contrast, the literature catalyst has poor activity for *ortho*-deuteration. However, through a simple modification of the literature synthesis[10] of this material (replacement of the THF reaction solvent with dichloromethane, a less coordinating solvent known to stabilise iridium dihydrides[11]) we obtained a catalyst possessing good activity for the *ortho*-deuteration of benzanilide.

Finally, **1** has proved a practical and convenient catalyst for tritium-labelling applications, details of which will be reported elsewhere.

Acknowledgements

The authors would like to thank the Physical Sciences Group at AstraZeneca R&D Charnwood together with J. P. Bloxsidge and R. G. B. Chaudry of the University of Surrey and H. Herman of Actinic Technology for their support with spectroscopic analysis.

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5. It is generally observed that such exchanges lead to complex mixtures in which the desired radiochemical constitutes less (often much less) than 50% of the radiolabelled products. For example, Wilkinson, D. J.; Hickey, M. J.; Kingston, L. P.; Mather, A. N. In *Synth. Appl. Isotop. Labelled Compd. Proc. Int. Symp.*; Dean, D. C., Filer, C. N., McCarthy, K. E., Eds.; John Wiley & Sons Ltd, 2004; Vol. 8, pp 47–50.
6. *Preparation of polymer catalyst 1.* (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (Crabtree's catalyst, 144 mg) was dissolved in dichloromethane (9 ml) and the resulting solution added to the polymer-bound triphenylphosphine (Aldrich item 3645, nominal 3 mmol of P per gram of resin, 60 mg). The reaction flask was then capped, flushed thoroughly with nitrogen and stirred for 2 h at ambient temperature. The orange supernatant was then decanted from the deep-red polymer and the polymer washed five times by resuspension and stirring in dichloromethane (4 ml each time). The supernatant was clear and colourless after the second wash. After drying to constant weight under vacuum a blood-red solid was obtained (89.3 mg). The catalyst showed no loss of activity when stored for 10 weeks under nitrogen at −20 °C. Only around 30% of the activity remained after the same period when stored in air at room temperature.
7. Polystyrene-based 'Polymer-bound' triphenylphosphine is available from many suppliers. During the course of these studies active catalysts were successfully prepared from Aldrich items 3645, 36,645-5, Fluka item 93093, Argonaut item 800378 and Jandagel (Aldrich item 53,341-6).
8. [2,6-D_2]Benzoyl[2,6-D_2]aniline, [2,6,2′6′-D_4]benzanilide. A solution of benzanilide (0.05 mmol ml^{-1}) was prepared in dichloromethane and an aliquot (0.5 ml) of this solution was added to catalyst **1** (6 mg) contained in a 10 ml capacity septum-sealed tube (CEM Corporation) containing a magnetic stirrer-bar. The tube was capped, evacuated, flushed with deuterium gas, re-evacuated and re-filled with deuterium. The tube was then stirred at ambient temperature for 4 h. At this point the tube was re-evacuated, re-filled with fresh deuterium and then stirred for a further 18 h. The resulting solution was filtered through a small plug of paper tissue in a Pasteur pipette and both the tube and pipette washed with dichloromethane (1 ml). After removal of the solvent under a stream of nitrogen [2,6,2′6′-D_4]benzanilide (4.6 mg, 91%) was obtained as a white solid, pure by TLC and HPLC–MS. ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (1H, t, $J = 7.5$ Hz), 7.38 (2H, d, $J = 7.5$ Hz) 7.46–7.6 (2H and 1H, complex) ppm ^2H NMR (77 MHz, $CHCl_3$) δ 7.70 and 7.95 (singlets, 1:1 ratio) ppm, MS (CI) gives 202.117 amu, $C_{13}H_8D_4ON$ requires 202.116 amu. The atom% deuterium abundance from MS was 93% (calculated for four positions). A single recrystallisation from water gave large crystal plates, mp. 164–165 °C (unlabelled mp 162–164 °C).
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