SHORT PAPER

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A novel microwave-activated Sonogashira coupling reaction and cleavage using polyethylene glycol as phase-transfer catalyst and polymer support†

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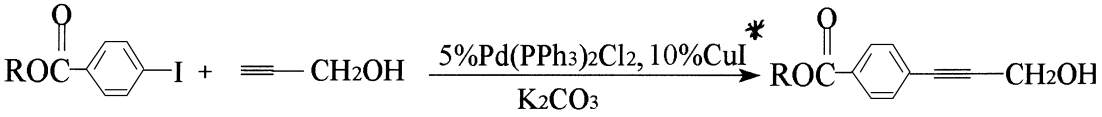
Under microwave-activation polyethylene glycol bound 4-iodobenzoic acid could be readily reacted with various terminal alkynes in excellent yields and purity using polyethylene glycol (PEG) as a solid-liquid phase-transfer catalyst and polymer support; the cleavage could be dramatically accelerated under microwave activation.

Keywords: Sonogashira coupling reaction, polyethylene glycol

Sold-phase synthesis of small molecules offers significant advantages over many conventional solution-phase routes to some compounds. However, such an approach requires a great deal of development time and effort to work up synthetic conditions on solid support. Recently, liquid-phase methodology provides an alternative to the solid-phase strategy,[1] utilising soluble polymers as supports. Due to the solubility of supports, the reactions are carried out under homogeneous conditions and the analysis of the supported intermediates and products can be done by routine methods. After reactions, purification is readily performed by preicitation and washing with ether.

Microwave-activated organic synthesis has become an increasingly used technique for the generation of new molecules.[2] Many solvent-free reactions using microwaves have been developed since it reduces the risks of hazards by pressure build-up in the reaction vessel and the scale-up is made easier. One particularly attractive field is the coupling of microwave activation (M.W.) with the solvent-free phase-transfer catalysis (PTC).[3] PEG has been investigated as a thermally stable, recoverable, inexpensive and nontoxic PTC, presumably operating by the same mechanism as crown ethers.[4] Recently, it has been reported that PEG bound substrates could also play the role of PTC in some reactions,[5] especially by Lamaty and coworkers who reported that amino acid derivatives could be generated sunder solvent-free microwave heating on the PEG supported Schiff's base protected glycine by alkylation using PEG support as the PTC and solvent.[6] Although there have been many cases involved with the synthesis of small compounds on PEG support,[1] there has been no report on the solvent-free formation of C–C bonds on PEG supports by transitional metal catalysis under microwave activation. In connection with our research on the transition metal catalysed reactions on soluble polymers,[7] we report here the first example of the microwave activated Sonogashira reaction under solvent-free solid-liquid phase-transfer catalysis conditions using PEG 4000 as the solvent and polymer support.*

We took propargyl alcohol as the terminal alkyne for the investigation (Scheme 1). We compared the reactions of methyl 4-iodobenzoate (**1**) and PEG 4000 bound 4-iodobenzoic acid (**2**) under different methods and conditions. *After three-times esterifying PEG 4000 with 4-iodobenzoic acid using DCC/DMAP in anhydrous dichloromethane, we obtained the immobolised PEG 4000 linked 4-iodobenzoic acid quantitatively, which had a loading value of 0.5mmol/g (determined by ^{1}H-NMR in DMSO-d_6).[8] A comparison was taken between 0.5g PEG linked 4-iodobenzoic acid and 0.25mmol methyl 4-iodobenzoate. By transesterification with MeOH in the presence of MeONa, the PEG bound substituted alkyne intermediate was completely released from the support to provide the product of the methyl ester. The yields were approximately equal for methods A and B (see Scheme 1), but the reaction time was greatly shortened from 3 hours to just 1.5 minute for traditional heating and microwave heating, respectively. The yield of method C which used silica gel as



R=Me (**1**) R=PEG (**2**) (PEG 4000 with double terminal hydroxy groups)

Method	Condition	Yield(%) (referred to methyl ester)
A	**2**/CH_3CN/50℃, 3h	92
B	**2**/solventless/M.W. 460w, 1.5min.	89
C	**1**/solventless, silica gel/M.W. 460W, 1.5min.	68

Scheme 1

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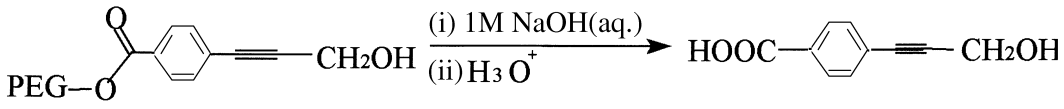
† This is a Short Paper there is therefore no corresponding material in *J. Chem. Research (M).*

*See **Caution** in Experimental Section



(**3**) (**4**)

Method Conditions

D traditional heating/50℃, 8h

E microwave heating/600W, 2min.

Scheme 2

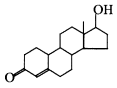
inorganic support was moderate. However, it was relatively low compared with that of method B. As we knew that yields could be dramatically improved under PTC coupled with microwave activation in solvent-free reactions,[3] it seemed from the result that PEG 4000 linked substrate of 4-iodobenzoic acid played the role of sold-liquid phase-transfer catalyst in this case, using potassium carbonate as base. It was indicated that due to the role of PEG support as PTC, the coupling reaction could be carried out in high yields rapidly under microwave activation.

Generally, the cleavage of products from PEG support in most reactions was achieved by saponification and then acidification. There have been many reports that saponification can be performed in short time and high yields under PTC, coupled with microwave activation.[9] Since the PEG support played the role of PTC as well, we expected that the cleavage of products from the support by saponification could be carried out under microwave activation with excellent results. We studied the intermediate of the PEG linked substituted alkyne (**3**) (Scheme 2). In the traditional heating method D, it took 8 hours at 50°C for the completion of cleavage (tested by TLC with disappearance of start material after acidification). Using the microwave heating method E, the release was finished in just 2 minutes in this open system. It was obvious that the microwave activated cleavage was highly efficient. To our knowledge, however, there has been no report on the microwave activated release of products from a PEG supports. We provide here a novel way for the rapid and efficient cleavage of products from a PEG support under microwave heating.

Based on the above finding, we extended the two-step microwave activated solvent-free Sonogashira coupling reaction and cleavage of products to other terminal alkynes (Scheme 3)*. The results are shown in Table 1. These indicated that the two-step microwave activated coupling and release reactions offered high yields from the terminal alkynes involved, even for norethindron with its bulky group (entry **h**). Due to the strategy of liquid-phase synthesis, excellent purity could be obtained through easy precipitation with ether and washing.

* See **Caution** in Experimental section.

Table 1 Microwave activated coupling and cleavage reactions on PEG 4000 support[a]

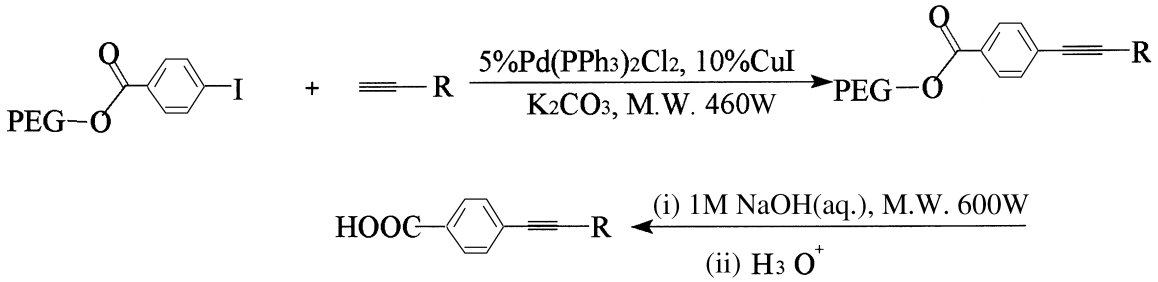
Entry	R	Observed MS (base molecule ion)		Yield/%[b]	Purity/%[c]
a	C_4H_9	129	202	87	–100
b	C_5H_{11}	129	216	87	–100
c	C_6H_{13}	129	230	84	96.03
d	CH_2OH	131	176	89	93.90
e	C_6H_5	222	222	94	95.45
f	$CH_3C_6H_4$	236	236	92	–100
g	$CH_2OC_4H_9$	159	232	90	98.33
h		227	418	85	96.88

[a]See **Caution** in experimental section. The microwave activated coupling reaction was carried out with 0.5 g (0.25 mmol) PEG 4000 linked 4-iodobenzoic acid, 0.5 mmol terminal alkyne and 1.0 mmol potassium carbonate under microwave heating (460 W) for 1.5 minute while the microwave activated cleavage reaction was carried out with IM NaOH aqueous solution under microwave heating (600 W) for 2 minutes;
[b]based on the original loading capacity of PEG 4000 with 0.5 mmol/g;
[c]based on the analysis by HPLC

In summary the two-step microwave activated coupling and cleavage reactions not only dramatically shortened the reaction times and obviously improved the yields, but also provided excellent purity, due to the triple roles of PEG 4000 as phase-transfer catalyst, solvent and polymer support. It is a novel way for the preparation of substituted alkynyl benzoic acids with efficient reaction times, yields, separation and purification.

Experimental

Caution: the inorganic base, catalysts and PEG 4000 bound 4-iodobenzoic acid must be well distributed by previously grinding into powder in order to avoid the destruction of the reaction vessel! Appropriate precautions should be taken.



Scheme 3

General: ^{1}H-NMR spectra were performed on a Bruker AM-500Hz spectrometer using TMS as internal standard; microanalysis was performed on a Carlo Erba 1106 analyser; IR spectra were recorded on a PK1600 FTIR-type spectrophotometer; MS spectra were determined on a HP 5989B spectrometer; HPLC was carried out on a HP 1100 analyser; melting points were not corrected.

General procedure for the microwave activated Sonogashira coupling reaction on PEG 4000 linked 4-iodobenzoic acid: In an open Pyrex glass vessel fitted with a septum (punctured by an 18 gauge needle), the terminal alkyne (0.5 mmol) was added to the well mixed powder of $Pd(PPh_3)Cl_2$ (5% mmol, 0.09 g) CuI (10% mmol, 0.05 g), K_2CO_3 (1 mmol, 0.138 g) and PEG 4000 bound 4-iodobenzoic acid (0.25 mmol, 0.5 g). The mixture was stirred thoroughly with a spatula for a few seconds and then was placed into the microwave oven for heating at a frequency of 2450 Hz and a power of 460 W for 1.5 minutes. After cooling, the PEG 4000 linked alkyne intermediate was dissolved in toluene and then filtered. The filtrate was precipitated with Et_2O and the resultant solid was washed with Et_2O several times. The intermediate was dried *in vacuo* for the next step.

General procedure for the microwave activated cleavate of product from the PEG 4000 bound alkyne intermediate: In an open pyrex vessel fitted with a septum (punctured by an 18 gauge needle), the PEG 4000 linked alkyne intermediate (0.25g) was dissolved in 1M NaOH aqueous solution (3ml). The solution was heated under microwave irradiation at 600 W for 2 minutes. After cooling, the solution was acidified with 5N HCl aqueous solution to within pH 3–4. The mixture was extracted with Et_2O and the organic layer was dried over anhydrous $MgSO_4$ to afford the product of alkynyl benzoic acid by removal of solvent.

Entry **a**: m.p. 122–124°C ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 0.96(t, *J*=7.3Hz, 3H), 1.49(m, 2H), 1.61(m, 2H), 2,45(t, *J*=7.0Hz, 2H),7.48(d, *J*=8.5Hz, 2H) FT-IR(KBr) (cm^{-1}) 3060, 2953, 2869, 2670, 2548, 2252, 1688, 1606, 1425, 1317, 1281, 1120, 908, 732, MS *m*/*z* (%) 202(M$^+$, 45) 187(45), 173(10), 159(50), 142(20), 129(100), 115(52), 102(60), 91(6), 77(18) Anal. calcd. for $C_{13}H_{14}O_2$ C 77.22, H 6.93; Found C 77.08, H 6.88

Entry **b**: m.p. 137–138°C ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 0.93(t, *J*=7.2Hz, 3H), 1.38(m, 2H), 1.45(m, 2H), 1.62(m, 2H), 2.44(t, *J*=7.0Hz, 2H), 7.47(d, *J*=8.5Hz, 2H), 8.03(d, *J*=8.5Hz, 2H) FT-IR(KBr) (cm^{-1}) 2930, 2862, 2667, 2549, 2240, 1865, 1605, 1428, 1317, 1296, 1125, 861, 771 MS *m*/*z* (%) 216(M$^+$, 45), 201(10), 187(65), 171(12), 159(40), 143(30), 129(100), 115(60), 91(15), 77(18) Anal. calcd. for $C_{14}H_{16}O_2$ 77.77, H 7.41; Found C 77.71, H 7.32.

Entry **c**: m.p.149–152°C ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 0.91(t, *J*=7.3Hz, 3H), 1.33(m, 4H), 1.47(m, 2H), 1.62(m, 2H), 2.45(t, *J*=7.0Hz, 2H), 7.48(d, *J*=8.3Hz, 2H), 8.03(d, *J*=8.3Hz, 2H) FT-IR(KBr) (cm^{-1}) 3050, 2931, 2855, 2667, 2548, 2218, 1686, 1606, 1424, 1315, 1294, 1120, 942, 859, 772, 722, 693 MS *m*/*z* (%) 230(M$^+$, 32), 201(28), 187(45), 159(37), 143(31), 129(100), 115(58), 91(15), 77(14) Anal. calcd. for $C_{15}H_{18}O_2$ C 78.26, H 7.83; Found C 78.14, H 7.71.

Entry **d**: m.p. 222–224°C (Lit.[10] 224–225°C) ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 4.40(s, 3H, 7.47(d, *J*=8.5Hz, 2H), 8.06(d, *J*=8.5Hz, 2H) FT-IR(KBr) (cm^{-1}) 3060, 2919, 2671, 2552, 2227, 1682, 1606, 1427, 1284, 1028, 949, 862, 771, 720, 693 MS *m*/*z*(%) 176(M$^+$, 48), 159(10), 131(100), 103(41), 77(36).

Entry **e**: m.p. 220–222°C (Lit.[11] 221°C) ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 7.20–7.64(m, 4H), 7.47(d, *J*=8.5Hz, 2H), 8.04(d, *J*=8.5Hz, 2H), FT-IR(KBr) (cm^{-1}) 3066, 2677, 2552, 2210, 1688, 1605, 1430, 909, 863, 772 MS *m*/*z* (%) 222(M$^+$, 100), 205(40), 176(37), 151(18).

Entry **f**: m.p. 242°C ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 2.27 (s, 3H), 7.13–7.62(m, 4H), 7.48(d, *J*=8.3Hz, 2H), 8.01(d, *J*=8.5Hz, 2H) FT-IR(KBr (cm^{-1}) 3040, 2920, 2671, 2548, 1686, 1606, 1420, 866 MS *m*/*z* 236(M$^+$, 100), 219(40), 189(22), 176(10) Anal. calcd. for $C_{16}H_{12}O_2$ C 81.35, H 5.08; Found C 81.31, H 517.

Entry **g**: m.p. 202–204°C ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 0.95(t, *J*=7.2Hz, 3H), 1.43(m, 2H), 1.62(m, 2H), 3.60(t, *J*=7.0Hz, 2H), 4.39(s, 2H), 7.48(d, *J*=8.5Hz, 2H), 8.06(d, *J*=8.5Hz, 2H) FT-IR(KBr) (cm^{-1}) 3062, 2956, 2871, 2676, 2555, 2249, 1686, 1607, 1430, 1320, 1283, 1097, 909, 862, 770, 725, 693 MS *m*/*z* (%) 232 (M$^+$, 3), 2 03(5), 189(55), 159(100), 131(65), 115(57), 103(15), 77(20) Anal. calcd. for $C_{14}H_{16}O_3$ C 72.41, H 6.90; Found C 72.33, H 6.78.

Entry h: m.p. >300°C ^{1}H-NMR(500MHz,$CDCl_3/D_2O$) (ppm) 0.98 (s, 3H), 0.88–2.41 (m, 24H), 5.85(s, 1H), 7.47(d, *J*=8.5Hz, 2H), 8.04(d, *J*=8.5Hz, 2H) FT-IR(KBr) (cm^{-1}) 3421, 3030, 2928, 2855, 2362, 1700, 1654, 1606, 1407, 1262, 1119, 861, 773, 726, 694 MS *m*/*z* (%) 418(M$^+$, 7), 400(3), 373(15), 277(100), 231(12), 199(31), 188(24), 129(24), 115(25), 91(39), 77(47) Anal. calcd. for $C_{27}H_{30}O_4$ C 77.51; H 7.18; Found C 77.43, H 7.03.

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