PS-IIDQ: an efficient polymer-supported amide coupling reagent

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Polystyrene-IIDQ is a polymer-supported coupling reagent that couples carboxylic acids to amines in good yields and high purity without the requirement of a pre-activation step. Importantly the order of addition of the amine, acid or coupling agent makes no difference to the efficiency of the coupling reaction and the reagent can be readily regenerated.

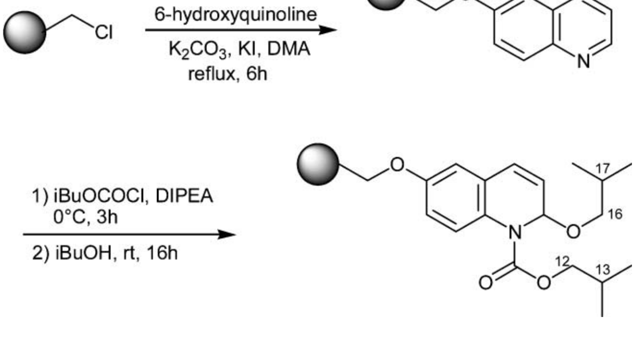
Many coupling reagents have been reported since the 1960's and used with varying degrees of success.[1] Classical methods using a variety of carbodiimides have been supplemented with a range of additives such as HOBt[2] and HOAt,[3] which enhance coupling efficiency and reduce racemisation. Newer reagents are often based on these additives and uronium or phosphonium salts, and include PyAOP,[4] PyBOP,[5] HATU,[6] HBTU.[7] Some work very efficiently with unhindered substrates but many have issues with stability,[8] and many of these newer agents give unwanted guanidinium species. Other coupling reagents such as those based on the generation of acid chlorides or bromides have therefore been synthesised such as PyBroP[9] or BOP-Cl[10] but have the major drawback of giving high racemisation rates. Recently some coupling agents have been made available on solid supports, including a number of supported carbodiimides.[11] Reagents such as polymer supported TBTU have also been attached to the resin *via* resin immobilised HOBt,[12] although the mode of action of these coupling agents means that by-products from the coupling agent will end up in solution. Other coupling agents can be used and include reagents which generate mixed anhydrides as the active coupling species. Among this family of coupling reagent is IIDQ (2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline) which has long been used in solution-phase synthesis,[13] although it has seen limited use in parallel synthesis. IIDQ however has several advantages over other coupling agents that include: the order of addition of the amine, acid and IIDQ makes no difference to the efficiency of coupling (no pre-activation step is needed); no guanidinium species can be obtained in contrast to the uronium based coupling reagents and IIDQ is stable in the presence of base. With these issues in mind a polymer-supported equivalent of IIDQ was targeted.

Polymer-supported IIDQ was successfully synthesised in three steps as shown in Scheme 1. 6-Hydroxyquinoline was coupled onto Merrifield resin using potassium carbonate (in excess) in DMA at reflux for 6 h (DMF should be avoided as this undergoes decomposition into primary amines that reacts with Merrifield resin).† By nitrogen and chlorine combustion elemental analysis conversion was 98%. PS-Quinoline was treated with isobutyl chloroformate in the presence of Hünig's base at 0 °C for 3 h, yielding a highly reactive intermediate which was quenched by the addition of isobutanol yielding the expected PS-IIDQ.‡ The presence of a tertiary amine base was essential as the reaction failed in the presence of K_2CO_3 or $NaHCO_3$, while organic bases such as pyridine did not work.

The MAS-^{1}H NMR spectra of polymer supported quinoline (Fig. 1b) and the supported IIDQ (Fig. 1c) were compared to the 1H NMR spectra of IIDQ (Fig. 1a). ^{1}H–^{1}H COSY spectra confirmed the correlation between the protons H-12 (and H-16) and the proton H-13 (and H-17 respectively) of the supported IIDQ and clearly showed that polymer-supported quinoline and polymer-supported IIDQ were successfully synthesised. This was confirmed by the characteristic absorption band of the carbamate moiety in the IR spectra at 1709 cm^{-1}. The loading of the resin obtained was evaluated by coupling benzylamine to phenylacetic acid and the isolated yield gave a loading of 1.6 mmol g^{-1}, corresponding to a conversion of 86% from Merrifield resin into the polymer-supported IIDQ.

The coupling conditions for PS-IIDQ were first optimised by coupling benzylamine to phenylacetic acid and DCM gave the best results. However the choice of DCM was not optimal because too many carboxylic acids were not soluble in this solvent and it was too volatile for parallel synthesis use and thus acetonitrile was chosen. Only 2 equiv. of PS-IIDQ were necessary to ensure high conversion and an excessive coupling time of 24 h was used in order to enable difficult substrates to react. This contrasts with many coupling reagents, which although often having a very high intrinsic reactivity are unstable in solution, with most of the reagent (or active HOBt ester) having degraded after an hour, a characteristic which is unsuitable for hindered substrates or if the coupling is slow. Considering this problem, PS-IIDQ offers a good balance between reactivity and stability.

PS-IIDQ was tested on a small library of 3 amines and 3 carboxylic acids (Table 1)§ and the yields and purities were compared to IIDQ in solution. This library followed a short study



Scheme 1 Synthesis of PS-IIDQ.

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Table 1 Coupling using PS-IIDQ or IIDQ

			PS-IIDQ		IIDQ	
Entry	Amine	Acid	Yield (%)[a]	Purity(%)[b]	Yield (%)[a]	Purity (%)[b]
1	4-*t*Bu-aniline	Boc-Aib-OH	69	100	81	91
2	Benzylamine	Boc-Aib-OH	66	100	92	98
3	H-PhG-OMe	Boc-Aib-OH	64	100	89	98
4	4-*t*Bu-aniline	Phenylacetic acid	60	100	83	98
5	Benzylamine	Phenylacetic acid	80	100	74	96
6	H-PhG-OMe	Phenylacetic acid	61	99	84	96
7	4-*t*Bu-aniline	Benzoic acid	89	100	78	93
8	Benzylamine	Benzoic acid	85	100	85	96
9	H-PhG-OMe	Benzoic acid	75	99	81	94

[a] Isolated yield. [b] Purity determined by ELSD. PhG = Phenylglycine.

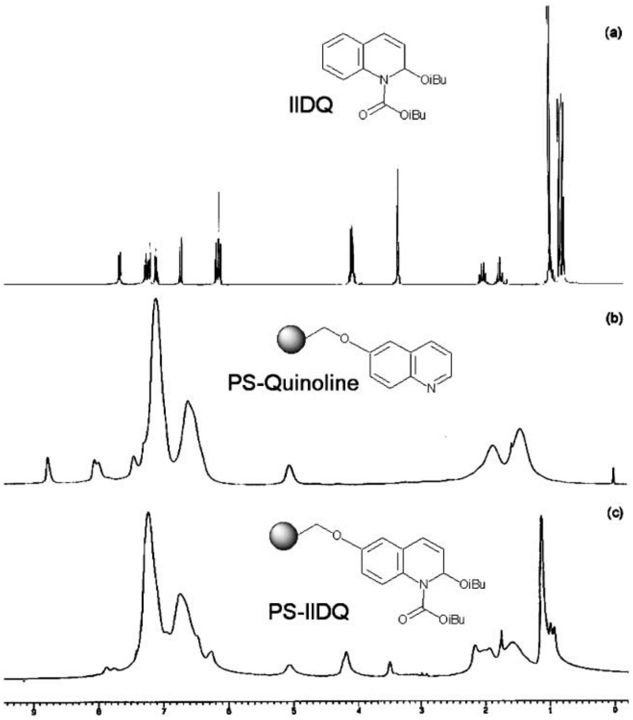

Fig. 1 NMR spectra at 400 MHz showing evidence of the synthesis of PS-IIDQ.

on the efficiency of IIDQ in solution, which proved that this coupling reagent was more efficient for general amide bond formation than many classic agents (HATU, BOP-Cl, PyBOP), when adding all the reactants at the same time. Synthesis comparing PS-IIDQ and IIDQ was carried out using the optimised conditions and, after reaction, a quick aqueous work-up was carried out in order to remove the unreacted amine and carboxylic acid.

The different amides were in most cases obtained in acceptable yield and very high purity. The coupling with sterically hindered building blocks phenylglycine (entries 3, 6 and 9) was successful even when coupling to hindered Boc-aminoisobutyric acid. Interestingly, coupling using an aniline succeeded in good yield (entries 1, 4 and 7). Generally results were slightly better in terms of purity when using PS-IIDQ. This illustrates the advantage of PS-IIDQ over the classic solution-phase reagent IIDQ, where an intensive work up is necessary to remove all the quinoline generated during the coupling.

Although PS-IIDQ was targeted for general amide bond formation, possible racemisation by epimerisation was evaluated with the Anteunis's test.[14] Thus coupling between Z-Gly-Phe-OH and H-Val-OMe gave the expected tripeptide with no epimerisation (limit of detection by ^{1}H NMR at 400 MHz), thus making PS-IIDQ a suitable reagent for coupling amino-acids.

In conclusion PS-IIDQ is an efficient polymer-supported coupling reagent for general amide bond formation, including hindered substrates. PS-IIDQ proved to be stable under general laboratory storage, with no degradation noticed after 2 months. In addition PS-IIDQ was easily regenerated, intensive washing followed by reaction with isobutyl chloroformate‡ yielded a recycled polymer-supported IIDQ with an efficiency similar to the original material. The resin (30 g) was recycled twice with little variation observed in the loading (1.5 to 1.6 mmol g^{-1}) and no changes in synthetic efficiency.

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Notes and references

† Procedure for synthesising PS-Quinoline: Merrifield resin (20 g, 3.99 mmol g^{-1}, 1 equiv.) was swollen in DMA (250 mL). 5 Equiv. of K_2CO_3, 2.5 equiv. of 6-hydroxyquinoline and a catalytic amount of KI were added and the reaction was heated at reflux for 6 h. The resin was filtered and washed successively with THF–H_2O (1 : 1), THF, DCM, MeOH, DCM, MeOH, Et_2O. Loading determined by Nitrogen Elemental Analysis: 2.74 mmol g^{-1} (98%).

‡ PS-Quinoline (25 g, 2.74 mmol g^{-1}, 1 equiv.) was swollen in dry DCM (300 mL). 3 Equiv. of dry DIPEA were added and the mixture was shaken and cooled to 0 °C. 3 Equiv. of isobutyl chloroformate were added to the reaction mixture. After 3 h, isobutanol (150 mL) was added, the mixture allowed to warm up and shaken overnight. The resin was then filtered and washed successively with 3 cycles of DCM, DCM–Et_2O, Et_2O. Loading evaluated by the yield of the coupling between benzylamine and phenylacetic acid: 1.6 mmol g^{-1}.

§ Typical procedure for using PS-IIDQ as coupling reagent: PS-IIDQ (1.60 mmol g^{-1}, 2 equiv.) was swollen in acetonitrile. The carboxylic acid (1 equiv.) and the amine (1 equiv.) were added and the reaction mixture was shaken for 24 h. The resin was filtered and washed with 3 cycles of DCM and MeOH. The filtrates were collected and concentrated *in vacuo*.

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