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A New Supported Reagent for the Photochemical Generation of Radicals in Solution

Lidia De Luca, Giampaolo Giacomelli,* Giancarlo Porcu, and Maurizio Taddei

Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2,
I-07100 Sassari, Italy

ggp@ssmain.uniss.it

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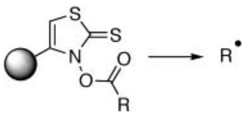
ABSTRACT



A new polymer-supported radical source was developed by loading an *N*-hydroxy thiazole 2(3)-thione on a Wang resin. This new supported reagent can be employed for a solid-phase version of the Hunsdiecker reaction or to liberate free alkoxy radicals, in a variant of the "catch and release" technique, under very mild conditions (irradiation with a discharge lamp) and simplifying the purification procedure.

The current development of new methods for the synthesis of organic molecules on a solid support has led to a renewed interest in a complementary technique in which a polymer-based reagent is employed to generate new products in solution. Polymer-supported reagents have been in use for the past 40 years. However, they are receiving considerable interest recently with the growth of high throughput solution-phase synthesis.[1] Parallel syntheses in solution using solid-supported reagents may be attractive because the reactions are often clean, it is possible to monitor the conversion using standard analytical techniques, and the final workup involves simple filtration and evaporation of the solvent. Polymer-supported reagents have been used in oxidations,[2] reductions,[3] halogenations,[4] and coupling reactions[5] and as scavengers[6] or ligands.[7] Supported reagents for the generation of radicals in solution may be very useful in the synthesis of libraries in solution. Many reports describe a radical precursor attached to a resin[8] so that the radical acceptor or the Bu_3SnH, used in the cyclization reaction, can be washed off at the end of the reaction. Alternatively, supported triorganotin hydrides have been developed to avoid the problem of separation of the stannylated byproducts present in solution.[9]

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Additional examples of photocleavable linkers or linkers that can be cleaved under radical conditions have also been described.[10]

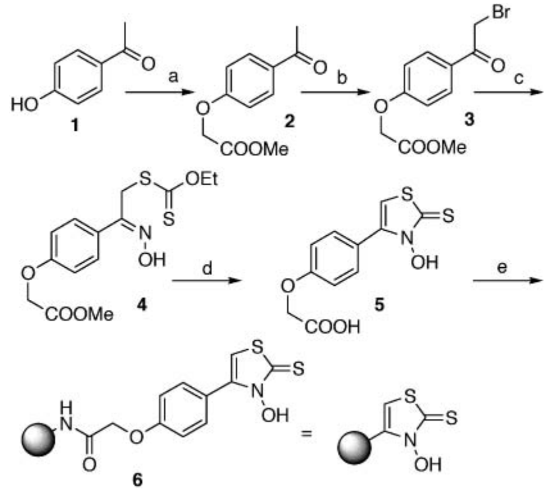
Following our interest in the discovery of new supported reagents,[11] we initiated a study of the development of a polymer-bound reagent that synthetically behaves in the same manner as the Barton−Crich thiohydroxamates.[12]

Since their discovery, *O*-acyl and *O*-alkyl thiohydroxamates have provided a mild and convenient source of C and O radicals which have been employed in the synthesis of different types of molecules.[13]

The major disadvantage of this versatile class of reagents is the formation of different mercapto heterocycles that must be separated from the product at the end of the reaction.[14] Loading a suitable thiohydroxamic derivative on a polymer support would allow the clean generation of radicals in solution.

The structure chosen to support the resin was an *N*-hydroxy thiazole 2(3)-thione (**5** in Scheme 1) as this kind of radical precursor is less light sensitive and the synthesis is more versatile than that of the well-known Barton *N*-hydroxy thiopyridones.[15]

Scheme 1[a]



[a] (a) $BrCH_2COOH$, NaOH, then MeOCOCl, Et_3N, DMAP, CH_2Cl_2 rt, 12 h; (b) Br_2, dry MeOH; (c) EtOCSSK, acetone, 0 °C, 5 h then rt for 12 h; $NH_2OH.HCl$, pyridine, MeOH, 0 °C; (d) $ZnCl_2$, 5 M in Et_2O, LiOH, MeOH/THF; (e) *N*-Fmoc-Gly-Wang resin, piperidine, DMF followed by HBTU, DIPEA, NMP, rt, 6 h.

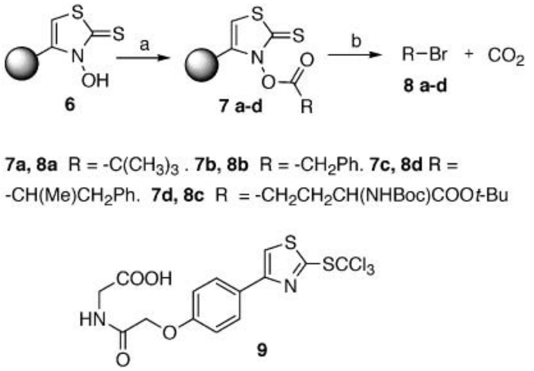
Thus, compound **5**, having a COOH group, was prepared in solution and subsequently loaded on an NH_2 terminal resin to give **6**. This approach simplified the procedure of monitoring the structure of the hydroxamic derivative and the effective loading on the resin. Resin **6** was prepared starting from 4-hydroxy acetophenone **1** (see Scheme 1). *O*-Alkylation of the phenolic hydroxyl group with bromoacetic acid followed by reaction with methyl chloroformate/DMAP gave **2** in 78% yield. α-Bromination with bromine in methanol gave **3** (86%) that was subsequently transformed into **4** with potassium *O*-ethylxanthate in acetone followed by treatment with hydroxylamine in pyridine (75% yield of the two steps).[16]

Cyclization of **4** was carried out with a saturated solution of $ZnCl_2$ in dry ether, and the final saponification with LiOH in MeOH/THF gave acid **5** in 66% yield.[17]

A Wang resin carrying *N*-Fmoc-Gly (loading reported from the supplier: 1.4 mmol/g) was deprotected under standard conditions, and acid **1** was coupled with the supported glycine under classical peptide coupling conditions. The reaction progress was monitored by using the ninhydrine test[18] (negative), and the loading, calculated on the basis of the amount of sulfur on the resin determined by microanalysis, was determined to be 1.2 mmol/g of dry resin.

To verify if **6** could be used to generate radicals in solution, we first prepared *O*-acyl thiohydroxamate **7a** (Scheme 2) by reaction of **6** with pivaloyl chloride in CH_2Cl_2 and in the presence of pyridine. The formation of the acyl derivative **7a** was determined with a colorimetric test based on the green color given to a resin containing an acid group by a solution

Scheme 2[a]



[a] (a) RCOCl, pyridine, rt, 6 h or RCOOH, HBTU, DIPEA, DMF, rt, 6 h; (b) $BrCCl_3$, benzene, 200 W lamp, 2 h.

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[17] **5**: mp 156−157 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 11.7 (bs, 1H), 9.0 (bs, 1H), 7.55 (d, 2H, $J = 8$ Hz), 7.00 (d, 2H, $J = 8$ Hz), 6.52 (s, 1H), 4.65 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 170.6, 159.1, 141.6, 130.0, 121.9, 114.8, 103.7, 65.1. Anal. Calcd for $C_{11}H_9N0_4S_2$ C, 46.63; H, 3.20; N, 4.94; S, 22.64. Found C, 46.50; H, 3.15; N, 4.77.

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of Malachite Green.[19] The hydroxamic resin **6** gave a positive test while that with **7a** was negative.

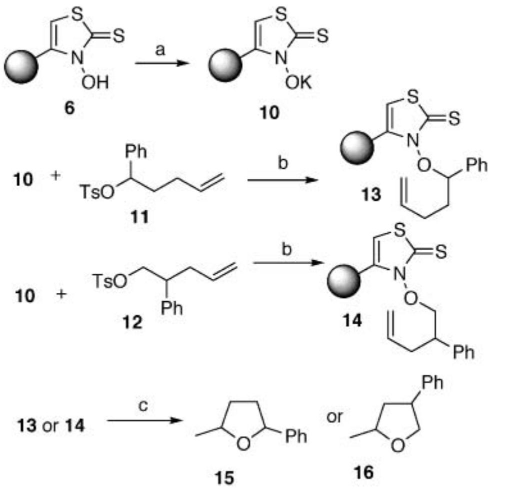
Resin **7a** was than dispersed in a 1:1 mixture of benzene and $CBrCl_3$ and irradiated with a simple 200-W discharge lamp while N_2 was bubbled through the solvent to effectively mix the reaction solution. The gaseous outcome was passed through a $Ba(OH)_2$ aqueous solution to monitor the formation of the CO_2 product during the expected Hunsdiecker reaction. After 20 min of irradiation, we observed the formation of the white precipitate of $BaCO_3$ and a gas chromatographic analysis of the solution showed the presence of *t*-BuBr **(8a)** showing that the *tert*-butyl radical was successfully generated.[20]

The same procedure was repeated to prepare compounds **7b**,**c** using phenylacetyl chloride and 2-methylbutanoyl chloride. Irradiation with a 200-W discharge lamp in the presence of $BrCCl_3$ gave bromides **8b**,**c**, which were obtained respectively in 65 and 62% yields. 4-Bromo-2-*tert*-butoxycarbonylaminobutanoic acid[21] **8d** was analogously obtained in 75% yield after loading *N*-Boc-glutamic acid to resin **6** with HBTU (*O*-benzotriazolyltetramethyluronium hexafluorophosphate) in NMP and DIPEA and irradiating the $BrCCl_3$ solution. The use of resin **6** makes the photochemical Hunsdiecker reaction very easy. After loading the acid on the resin, the reagents and the excess of the acid are eliminated by rinsing several times with CH_2Cl_2. During the reaction the formation of the desired bromide can be monitored using TLC or GC analysis. The product can be directly isolated in pure form (^1H NMR analysis, 300 MHz) after filtration of the resin and evaporation of the solvent.

A chain mechanism is implicated in this reaction with the formation of a trichloromethyl radical that is trapped on the resin. Thiazole **9** was indeed isolated after treatment with TFA/CH_2Cl_2 of the resin recovered at the end of the reaction.

Resin **6** was also used to generate alkoxy radicals in solution. Upon treatment of **6** with a solution of KOH in ethylene glycol, potassium salt **10** was formed. After discharging the solvent, tosylates **11** or **12** were added in DMF. The complete alkylation procedure is long (at least 3 days) but provides the desired hydroxamates **13** and **14** in almost quantitative yield.[22] Compound **13** and **14** were rinsed several times with DMF and CH_2Cl_2 and dried over P_2O_5 to give resins that were stable for at least 1 month if protected from light (Scheme 3).

Scheme 3[a]



[a] (a) KOH in $HOCH_2CH_2OH$; (b) pyridine, rt, 3 days; (c) benzene, 200 W lamp, *t*-BuSH, rt, 4 h.

The radical cyclization of compounds **13** and **14** was carried out in benzene by irradiating the mixture with a tungsten lamp (200 W) in the presence of *t*-BuSH as radical trap.

The progress of the reaction was monitored with TLC analysis in comparison with a solution of authentic samples of tetrahydrofurans **15** and **16**.[23] The transformation takes place in few hours, giving the expected *5-exo trig* cyclization. At the end of the reaction, products **15** and **16** were isolated in pure form (^1H NMR analysis, 300 MHz) after simple filtration of the resin and evaporation of the solvent. In this last case the overall process (linking the alkene to the resin followed by cyclization) may be considered as a variant of the "resin-capture-release" technique.[24]

In conclusion we have developed a new supported radical source that can be employed for a solid-phase version of the Hunsdiecker reaction or to liberate free alkoxy radicals that undergo cyclization reaction under very mild conditions (irradiation with a discharge lamp). This supported radical source allows isolation of the products of the radical reaction without the tedious and expensive chromatographic purifications generally required by *O*-acyl and *O*-alkyl thiohydroxamates that have prevented their use in high throughput synthesis so far. Although not described here, this new supported reagent can be used in automated parallel synthesis of products arising from C−O, C−N, or C−C bond-forming radical chain reactions.

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(19) Attardi, M. E.; Porcu, G.; Taddei, M. *Tetrahedron Lett.* **2000**, *41*, 7391−7394.

(20) **General procedure:** Resin **6** (0.2 g of a 1.2 mmol/g sample, 0.24 mmol), after swelling in NMP for 2 h, was rinsed several times with CH_2Cl_2 and added to a solution of pivaloyl chloride (0.2 g, 1.6 mmol) and pyridine (0.5 mL) in CH_2Cl_2 (5 mL) containing a catalytic amount of DMAP. After 2 h of stirring, a few beads were submitted to a Malachite Green test which was negative (gray beads). After the resin was rinsed several times with CH_2Cl_2, DMF, CH_2Cl_2, and benzene, a solution of $BrCCl_3$ (1 mL) in benzene (5 mL) was added. The flask was irradiated with a tungsten lamp (200 W) for 1 (h) During that period, N_2 was bubbled through the solution. After filtration, the amount of *t*-BuBr formed (approximatively 30 mg, 92% yield) was determined by GC analysis. Alternatively, evaporation of the solvent gave products **8b**−**d**. The GC analysis of *t*-BuBr can also be used as an indirect method to evaluate the loading of the resin.

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(22) The success of the reaction was determined by inspection of the FT-IR spectra of the beads that did not show any peak before 3000 cm^{-1}.

(23) Following the preparation described in the literature (Hartung, J.; Hiller, M.; Schmidt, P. *Chem. Eur. J.* **1996**, *2*, 1014−1023), **15** and **16** were always obtained as a mixture of diastereoisomers after two chromatographic separations.

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