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Chameleon catches in combinatorial chemistry: Tebbe olefination of polymer supported esters and the synthesis of amines, cyclohexanones, enones, methyl ketones and thiazoles

Christopher P. Ball,[a] Anthony G. M. Barrett,*[a]† Alain Commerçon,*[b] Delphine Compère,[a] Cyrille Kuhn,[a] Richard S. Roberts,[a] Marie L. Smith*[a] and Olivier Venier[a]

[a] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*
[b] *New Lead Generation, Rhône-Poulenc Rorer, Vitry, France*

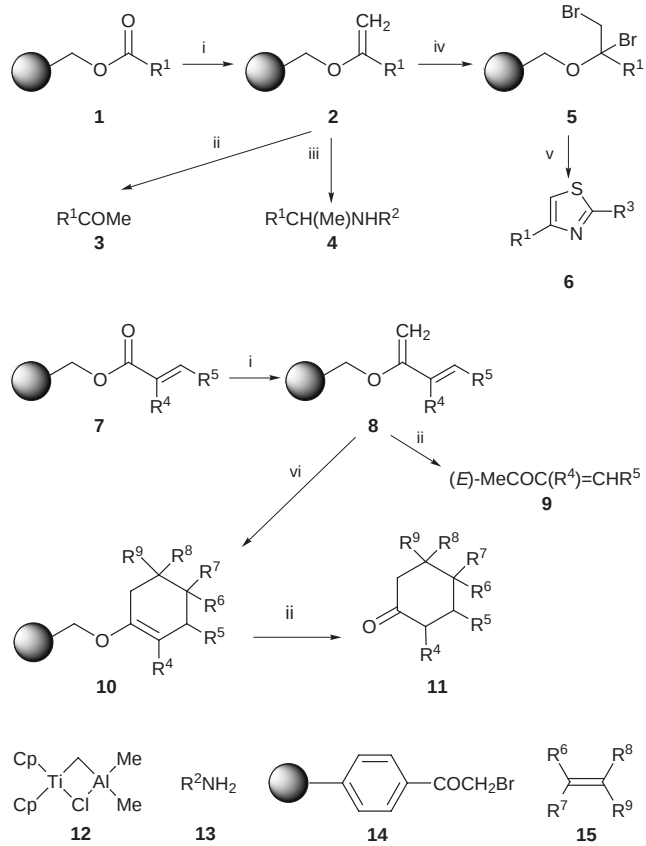
Tebbe olefination of supported esters $R^1CO_2CH_2$–polymer gave the corresponding vinyl ethers $R^1C(=CH_2)OCH_2$–polymer which were released, under acidic conditions, to produce methyl ketones R^1COMe; by reductive amination, to produce amines $R^1CH(Me)NHR^2$; by bromination and reaction of $R^1CBr(CH_2Br)OCH_2$-polymer with thioureas to produce thiazoles; or, for supported dienyl ethers derived from α,β-unsaturated esters, by Diels–Alder reaction and acid mediated cleavage to produce cyclohexanone derivatives.

Solid phase synthesis is invaluable for the construction of libraries of small organic compounds for biological evaluation.[1] Such bioassay is frequently carried out in solution using an appropriate enzyme or receptor. The method of attachment and detachment of the requisite substrates to the resin is critical. In many solid phase syntheses, the substrates are conveniently attached to the polymer support through a carboxylic acid function. This is readily achieved using supports including Merrifield, Wang and Tentagel resins *etc*.[2] Following substrate modification, cleavage affords a carboxylic acid, ester, amide or, *via* reductive cleavage, a primary alcohol. Methods that allow for the cleavage of resin bound carboxylate derivatives yet which access alternative and variable functionality would be extremely desirable. Herein we report the conversion of supported esters into enol ethers,[3] with subsequent on-resin functionalisation and detachment with amplification of diversity.

Methylenation of the resin bound esters **1**‡ with the Tebbe reagent[4] **12** (PhMe–THF 25 °C, 12 h) gave the corresponding vinyl ethers **2** (Scheme 1). The reaction mixtures were quenched with 15% aq. NaOH and the resin washed consecutively with THF, H_2O, EtOAc, EtOAc–MeOH (1:1) and MeOH followed by removal of solvent *in vacuo*. In this reaction, commercial Tebbe reagent (Aldrich) proved to be superior to either **12** generated *in situ*,[5] where premature cleavage from the support was a problem, or the Petasis reagent (Cp_2TiMe_2).[6] Hydrolysis (1 M H_2SO_4 in DMF or 1% TFA in CH_2Cl_2) of ethers **2** brought about cleavage from the resin and gave the corresponding ketones **3**§ (41–92%). Alternatively, acid mediated hydrolysis and reductive amination[7] using amine **13** and $NaBH(OAc)_3$ gave the corresponding amines **4**¶ (13–89%).

The ethers **2** were found to be useful intermediates for further transformations prior to detachment from the resin. Thiazoles, important pharmacophores with diverse biological activities,[8] are available from α-bromo ketones *via* the Hantzsch thiazole synthesis. Thus reaction of the vinyl ether **2** (R = Bn) with Br_2 (1 M in CH_2Cl_2, 2 equiv., 1 h) and washing (CH_2Cl_2) gave the corresponding supported dibromide **5** as indicated by the disappearance of the enol ether (IR), gel phase magic angle spinning ^1H NMR [400 MHz; $CDCl_3$: δ 4.25(CH_2Br)] and elemental analysis (loading 0.65 mmol g^{-1}). Reaction of the dibromide **5** (R = Bn) with thiourea (4 equiv., MeOH at reflux, 12 h), neutralisation (K_2CO_3), filtration with MeOH and evaporation gave thiazole **6** (R = Bn) contaminated with excess thiourea. This impurity was removed by reverse phase HPLC or, more simply, using the polymer supported α-bromo ketone scavenger **14**[9] (200–400 mesh, 0.96 mequiv.g^{-1}, 2 equiv.). Using either of these purification methods, thiazole **6** (R = Bn) was obtained in 40% yield based on the loading of the Merrifield resin (1.0 mmol g^{-1}) to which the phenylacetic acid had been attached. This methodology, which has been extended to a range of thiazoles **6**,‖ has the major advantage of starting from readily available carboxylic acids rather than less diverse commercial α-bromo ketones.

Tebbe methylenation of the resin bound α,β-unsaturated esters **7**[10]‡ (ν_{max}/cm^{-1} 1720–1740) gave the corresponding supported dienyl ethers **8** (1635–1650 cm^{-1}) which could be either hydrolysed (1% TFA in $CDCl_3$) to provide the enones **9**** or converted into the Diels–Alder adducts **10**. The diene



Scheme 1 *Reagents and conditions*: i, **12**, PhMe, THF, 25 °C; ii, 1% TFA, CH_2Cl_2, 25 °C; iii, 1 M H_2SO_4, DMF, then **13**, $NaBH(OAc)_3$, 25 °C; iv, Br_2, CH_2Cl_2 (1 M, 2 equiv.), 25 °C; v, R^3CSNH_2 (4 equiv.), MeOH, reflux, then **14** (2 equiv.), MeOH, reflux; vi, **15**, PhMe, 25 °C (maleimide) or 80–100 °C (other dienophiles)

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resins **8** may be stored for up to six months without loss of activity but were generally used directly. Diels–Alder reaction with *N*-methylmaleimide (PhMe, 25 °C) or 2-chloroacrylonitrile, methyl vinyl ketone, dimethyl fumarate or 2-ethylacrolein (PhMe, 80–100 °C) gave the immobilised cyclohexene derivatives **10**. Subsequent cleavage from the resin (1% TFA in CH_2Cl_2) gave the corresponding cyclohexanone derivatives **11**.†† We observed high *endo*-selectivity with *N*-methylmaleimide consistent with the solution phase reactions of 2-silyloxy dienes with maleimides[11] and in contrast with Diels–Alder reactions of resin bound 4-substituted 2-aminobutadienes.[12]

In summary, we have developed a novel detachment method for the removal of substrates from a solid support which allows for the concomitant introduction of further diversity. This strategy using chameleon‡‡ catches should be applicable to the generation of diverse libraries from polymer supported carboxylic esters. Further reactions of the supported enol ethers will be reported in due course.

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Notes and References

† E-mail: m.stow@ic.ac.uk

‡ The supported esters **1** and **7** were prepared from Merrifield resin (200–400 mesh, 1.0–1.7 mequiv. g^{-1}) (Cs_2CO_3, KI, DMF, 80 °C) [the Tebbe olefination chemistry in this paper has also been carried out on Wang resin (200–400 mesh, 0.7–1.13 mequiv. g^{-1})]. For an alternative synthesis of supported α,β-unsaturated esters see ref. 12. All syntheses in this paper were carried out both manually, using single bead FT-IR spectroscopy to follow reactions (**1** 1720–1740, **2** 1635–1645, **7** 1720–1740, **8** 1635–1650 cm^{-1}) and in a parallel fashion on a Nautilus™ 2400 Organic Synthesizer (Argonaut Technologies, Inc.). All the products were at least 90% pure (HPLC, GC–MS). All yields were determined with respect to the original loading of chloride for Merrifield resin.

§ The ketones **3** [R^1 (%)] were isolated by filtration and evaporation: $Me(CH_2)_6$ (87%); Ph (62%); 4-BrC_6H_4 (41%); 4-IC_6H_4 (71%); 4-$MeOC_6H_4$ (92%); 3-$MeOC_6H_4$ (56%); 2,4,6-$(MeO)_3C_6H_2$ (47%); 4-$MeOC_6H_4CH_2$ (74%); 4-PhC_6H_4 (65%) and 3-indolyl–CH_2CH_2 (74%).

¶ The amines **4** [R^1, R^2 (%)] were isolated by filtration, partition between Et_2O and 1 M NaOH, drying ($MgSO_4$) and evaporation: $Me(CH_2)_6$, Pr (13%); $Me(CH_2)_6$, cyclopropyl (19%); $Me(CH_2)_6$, allyl (27%); 4-$MeOC_6H_4CH_2$, Pr (89%); 4-$MeOC_6H_4CH_2$, cyclopropyl (85%); 4-$MeOC_6H_4CH_2$, allyl (89%); 3-indolyl–CH_2CH_2, Pr (65%); 3-indolyl–CH_2CH_2, cyclopropyl (61%); 3-indolyl–CH_2CH_2, allyl (79%).

‖ The thiazoles **6** [R^1, R^3 (%)] were isolated following purification using scavenger **14**: Ph, NH_2 (40%); Ph, NHMe (15%); Ph, NHBn (10%); Ph, Me (14%); 3-$MeOC_6H_4$, NH_2 (23%); 3-$MeOC_6H_4$, NHMe (15%); 3-$MeOC_6H_4$, NHBn (13%); $Me(CH_2)_6$, NH_2 (15%); $Me(CH_2)_6$, NHMe (10%); $Me(CH_2)_6$, NHBn (12%).

** The enones **9** [R^4, R^5 (%)] were quantified by cleavage (1% TFA in $CDCl_3$) and ^1H NMR with a $(Me_3Si)_2O$ reference: H, Ph (50%); H, Me (28%); H, Et (31%); H, Pr (33%); H, $Me(CH_2)_6$ (48%); $(CH_2)_4$ (53%).

†† The cyclohexanones **11** [R^4, R^5, dienophile, (%, diastereoselectivity)] were quantified by cleavage (1% TFA in $CDCl_3$) and ^1H NMR with a $(Me_3Si)_2O$ reference: H, Ph, *N*-methylmaleimide (30%, 97:3); H, Me, *N*-methylmaleimide (30%, 97:3); H, Et, *N*-methylmaleimide (18%, 97:3); H, Pr, *N*-methylmaleimide (27%, 97:3); H, $Me(CH_2)_6$, *N*-methylmaleimide (35%, 7:3); $(CH_2)_4$, *N*-methylmaleimide (51%, 97:3); H, Ph, (*E*)-$MeO_2CCH{=}CHCO_2Me$ (17%, 1:1); H, Ph, $H_2C{=}CClCN$ (23%, 7:3); H, Ph, $H_2C{=}CEtCHO$ (21%, 5:3); H, Ph, $H_2C{=}CHAc$ (44%, 7:3); H, Me, $H_2C{=}CHAc$ (11%, 5:3); H, $Me(CH_2)_6$, $H_2C{=}CEtCHO$ (19%, 3:1); H, $Me(CH_2)_6$, $H_2C{=}CEtAc$ (22%, 4:1); $(CH_2)_4$, $H_2C{=}CEtCHO$ (20%, 2:2:1:1); $(CH_2)_4$, $H_2C{=}CHAc$ (43%, 3:2).

‡‡ For other chameleons see refs. 13 and 14. Petasis has mentioned the possibility of the olefination of polymer supported peptides using Cp_2TiMe_2 but has yet to report any details: *Fifth Chemical Congress of North America*, Cancun, Mexico, November 13, 1997.

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