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Coupling reaction of chalcogenyl halides with alkynes on a solid support. Synthesis of new selenium-containing retinoids

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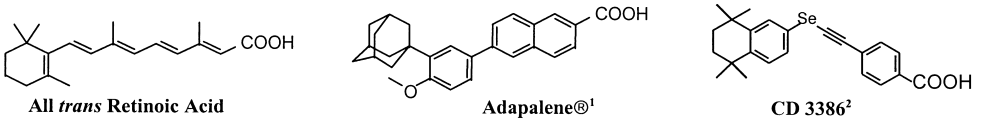
Abstract

A new series of selenium-containing acetylenic retinoids has been prepared by a copper assisted reaction of selenyl bromides with terminal alkynes bound to Wang resin.

Keywords: retinoids; selenium and compounds; solid-phase synthesis; alkynes.

Retinoids (Scheme 1), both synthetic[1,2] and natural analogues of retinoic acid, exert marked effects on cell differentiation and proliferation.[3] These properties confer on them a high potential for treatment of hyperproliferative disorders including acne, psoriasis and cancer.



Scheme 1.

Interest in the application of solid-phase synthesis for the generation of large diverse compound libraries for use in high-throughput screening has increased rapidly in the past few years.[4] The solid-phase synthesis is also used to optimize initial lead compounds.[5] In an earlier paper,[2] we reported the direct coupling of alkynylsilanes with selenylhalides to obtain selenium-containing acetylenic retinoids (**CD 3386**). Copper assisted reaction of chalcogenyl halide with terminal alkynes has been described in the liquid-phase,[6] but never in the solid-phase. Here, we have investigated the scope and limitation of a solid-phase preparative method for obtaining a small library of selenium-containing acetylenic retinoids, by reacting phenylchalcogenyl bromides

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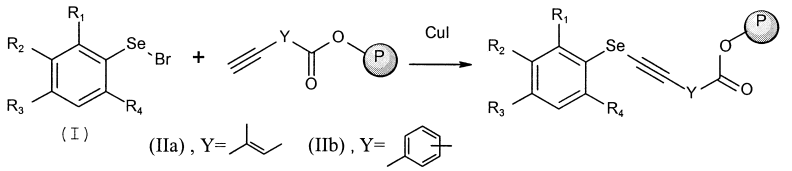
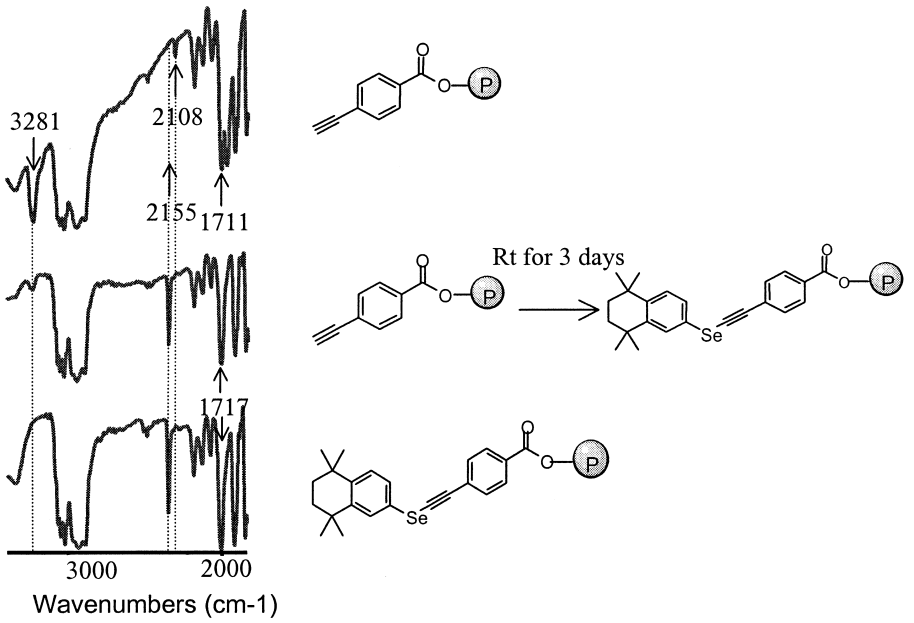
with terminal alkynes bound to Wang resin, in the presence of copper iodide, in order to optimize our lead compound **CD 3386** (Scheme 2).



Scheme 2.

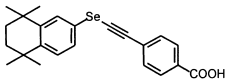
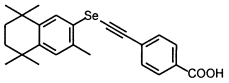
Commercial Wang resin was coupled with 4-iodobenzoic acid using diisopropylcarbodiimide and a catalytic amount of dimethylaminopyridine in dichloromethane at room temperature.[7] The corresponding terminal alkyne was obtained by palladium-catalyzed coupling with trimethylsilylacetylene ($PdCl_2(PPh_3)_2$, Et_3N, dioxane)[8] followed by desilylation using cesium fluoride in a mixture 2:1 of THF and methanol. The coupling reaction of the polymer bound terminal alkynes with selenyl bromide was monitored by FTIR (Scheme 3).



Scheme 3. The FTIR sample was collected on a spectrophotometer Nicolet 740; KBr pellet. IR absorbance bands attributable to disappearing alkyne at 3281 cm^{-1} and 2108 cm^{-1}, and emerging alkynyl selenide at 2155 cm^{-1} are highlighted as the dotted line. The carbonyl group moved from 1711 to 1717 cm^{-1}

When terminal alkynes were treated with 5 equiv. CuI(1), and 2.5 equiv. selenyl bromide at room temperature for 3 days, some unreacted alkyne was recovered (Table 1). Increasing the temperature to 60°C furnished the product with a lower yield than in a liquid-phase synthesis.[2]

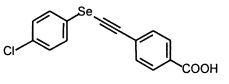
Table 1
Effect of temperature on the coupling conversion

Product	Conditions	Time	Conversion (FTIR) [a]	Conversion (HPLC) [b]	Isolated yield
	CuI/rt	3 days	Incomplete	14% / 86 %	Not done
	CuI/60°C	24 h.	Complete	0 % / 100 %	22 %
	CuI/rt	3 days	Incomplete	4% / 96 %	Not Done
	CuI/60°C	24 h.	Complete	0 % / 100%	28 %

a : disappearing alkyne and emerging alkynyl selenide were monitored by FTIR (Nicolet 740 ; KBr pellet). b : ratio of unreacted terminal alkyne / alkynyl selenide monitored by HPLC (RP 18), after cleavage (TFA 10% in DCM at R.T. for 7 minutes).

Therefore, the coupling reaction of the commercially available bis(4-chlorophenyl) diselenide was studied with different bases, to control the pH and to avoid premature cleavage (Table 2). Inorganic bases like Cs_2CO_3 were ineffective.

Table 2
Effect of a base on the coupling yield

Product	Conditions	Purity (HPLC)	Conversion (FTIR)	Isolated yield
	CuI / 60°C / 24h.	Not Done	Complete	20%
	CuI / 60°C / Cs_2CO_3 / 24h.	-	-	0%
	CuI / 60°C / Bu_3N / 24h.	92 %	Complete	44%

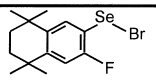
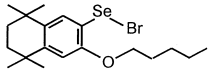
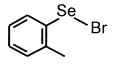
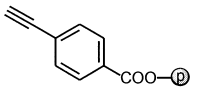
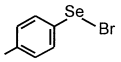
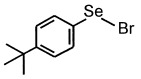
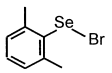
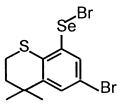
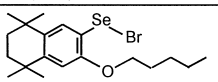
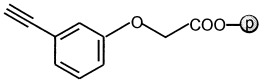
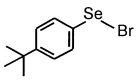
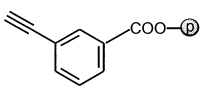
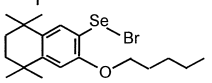
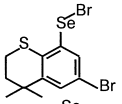
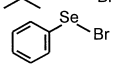
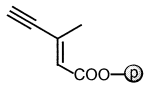
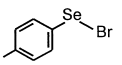
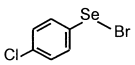
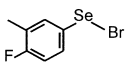
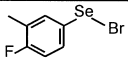
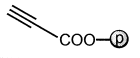
Treatment of the appropriate terminal alkyne with 5 equiv. CuI, 4 equiv. tributylamine and 2.5 equiv. selenyl bromide at 60°C for 24 h afforded the alkynyl selenide in good yield and purity. Cleavage from the resin was done under mild conditions: TFA 10% in DCM at rt for 7 min.

The procedure was used to generate a small library from which selected compounds are listed in Table 3. Commercial Wang resin was coupled with a series of acetylenic compounds using diisopropylcarbodiimide and a catalytic amount of dimethylaminopyridine in dichloromethane at room temperature to provide polymer bound terminal alkynes.[8] Final products were isolated and purified after cleavage, by crystallization in heptane, which explains the variability and the lower yields than those reported in Table 2.

Both series, aryl and enyne, worked well. The introduction on the lipophilic part of the molecule of alkyl groups such as methyl, *tert*-butyl or cycloalkyl, as well as halogen groups, had almost no influence. Presence of an alkoxy group decreased the yield and the purity of the isolated products. When the carboxyl group was moved from the *para*- to the *meta*-position relative to the alkyne, the yield of the reaction was slightly lower. When the carboxyl group was directly attached to the alkyne, the purity decreased and the reaction failed when benzoic acid was replaced by a phenoxy acetate moiety.

In conclusion, we have demonstrated that alkynyl selenides can be produced in good isolated yield and purity from polymer-supported alkynes and selenyl bromides. This methodology allows the straightforward introduction of various functionalities and appears to be useful for the production of libraries.

Table 3
Alkynyl selenides prepared according to the optimized procedure

Selenylbromide	Polymer bound alkyne[a]	Isolated yield	Purity of isolated products (HPLC)
		18 %	92 %
		5 %	59 %
		25 %	68 %
		12 %	80 %
		33 %	88 %
		35 %	93 %
		25 %	57 %
		—	—
		45 %	75 %
		8 %	56 %
		27 %	65 %
		34 %	79 %
		21 %	76 %
		38 %	79 %
		32 %	90 %
		28 %	45 %

a : Ⓟ = Wang resin.

Acknowledgements

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9. Typical coupling procedure: a mixture of bromoselenide (2 equiv.), CuI (5 equiv.), tributylamine (4 equiv.), resin-bound terminal alkyne in DMF was stirred at 60°C for 24 h. The resin was then washed with DMF, H_2O, THF, CH_2Cl_2.