

Report

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Photoinduced Cyclorelease for Condensed Heteroaromatic Synthesis

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Solid phase synthesis of heterocyclic compounds has been regarded as one of the important subjects in combinatorial chemistry.¹ Various reactions have been applied for solid phase heterocyclic synthesis, and among various strategies, cyclorelease is very attractive because only molecules that have gone through the whole reaction sequence necessary will be released.² On the other hand, palladium catalyzed cross-coupling reactions such as the Heck reaction have been introduced in solid phase synthesis as a powerful tool for carbon–carbon bond formation.³ To develop a new strategy for cyclorelease, Heck reaction using REM resin⁴ was investigated as a key reaction for constructing substrates for cyclorelease. Photoinduced cyclorelease was found to be useful for the synthesis of condensed heteroaromatics such as 2-quinolone and coumarin.

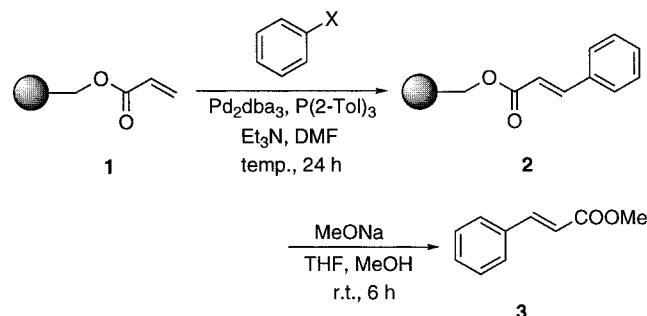
To examine the reactivity of REM resin as a coupling partner for Heck reaction, the reaction of halobenzenes with REM resin (**1**) was investigated. REM resin (**1**) was reacted with iodobenzene in the presence of Pd₂dba₃, P(2-Tol)₃, and Et₃N in DMF at various temperatures for 24 h (Scheme 1, Table 1). The cross-coupling reaction proceeded smoothly at the temperature between 40 and 100 °C, and methyl cinnamate was obtained in good yields after cleavage with sodium methoxide in MeOH–THF. Bromobenzene also reacted with **1** under similar reaction conditions; however, slightly higher temperature was required.

Our next interest was focused on cyclization, and the cross-coupling reaction of **1** with 2-iodoaniline (**4a**) and 2-iodophenol (**4b**) was carried out in order to prepare the substrates for photoinduced cyclorelease. The palladium

Table 1. Heck Reaction Using REM Resin

X	temp (°C)	yield (%)
I	rt	3
I	40	71
I	60	73
I	100	72
Br	40	49
Br	60	76

Scheme 1

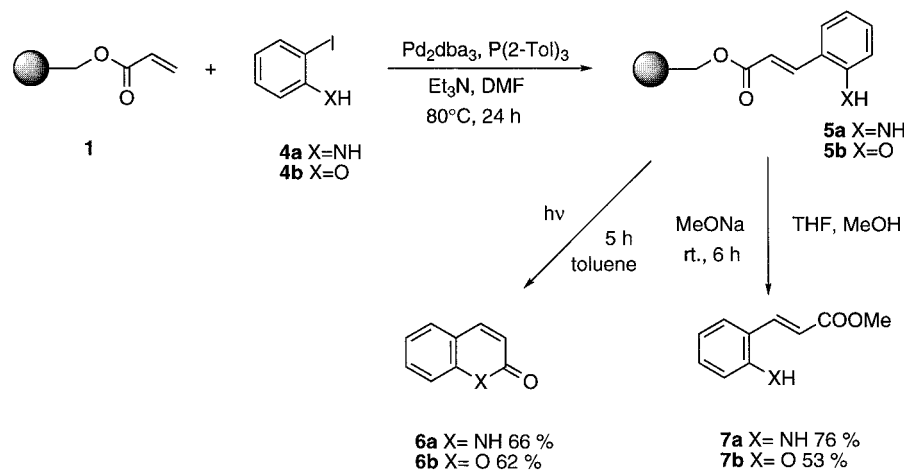


catalyzed reactions were performed under similar conditions at 80 °C for 24 h, and the immobilized ortho-substituted cinnamates were cleaved with sodium methoxide in MeOH–THF to give methyl 2-aminocinnamate in 76% yield and methyl 2-hydroxycinnamate in 53% yield, respectively (Scheme 2).

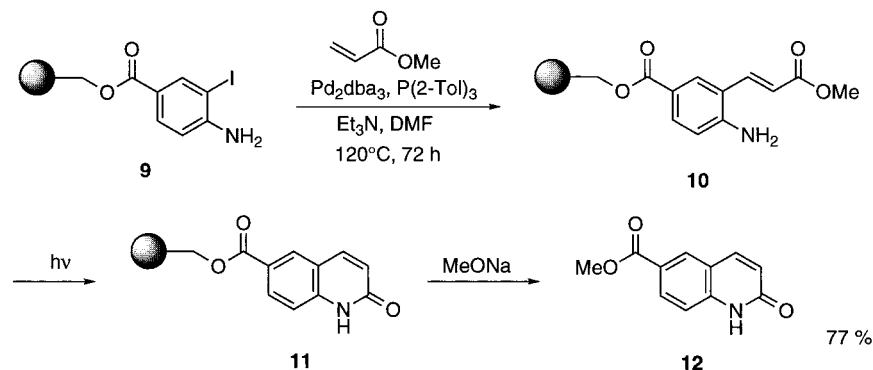
The immobilized ortho-substituted cinnamates were then subjected to cyclorelease under irradiation with a 400 W high pressure mercury lamp in toluene for 5 h. The photoisomerization of the olefin followed by cyclization gave 2-quinolone and coumarin in 66% yield and 53% yield, respectively (Scheme 2).

In addition to the cyclorelease, a noncyclorelease type photocyclization was also investigated using immobilized aminocinnamate. The immobilized 4-amino-3-iodobenzoate **9** was reacted with methyl acrylate in the presence of Pd₂dba₃, P(2-Tol)₃, and Et₃N in DMF at 120 °C for 72 h to give the immobilized cinnamate **10**. The photoinduced cyclization followed by the treatment with sodium methoxide

Scheme 2



Scheme 3



in MeOH–THF gave methyl 2-quinolone-6-carboxylate (**12**) in 77% yields (Scheme 3).

In summary, the solid phase cyclization of the immobilized 2-substituted cinnamate was found to be effective for condensed heteroaromatic synthesis. The photoinduced cyclorelease, in particular, is considered to be a new potential strategy for rapid synthesis of heterocyclic compounds.

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Supporting Information Available. Representative experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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