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Coupling of activated esters to gramines in the presence of ethyl propiolate under mild conditions

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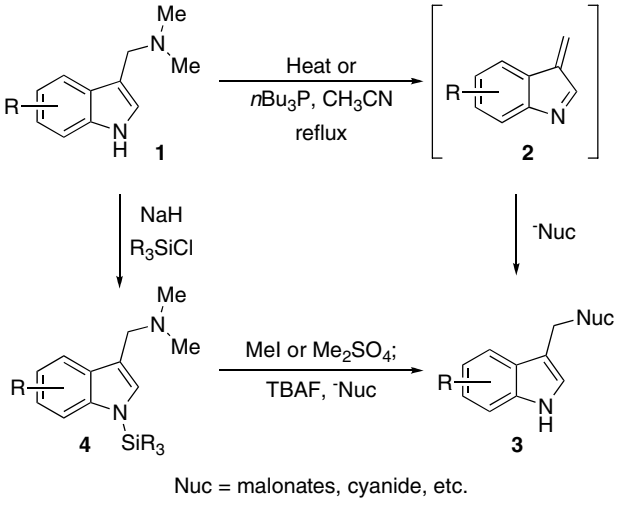
Abstract—The coupling of activated esters to gramine derivatives is described using ethyl propiolate. A series of substrates have been prepared using these mild conditions to provide a scope and limitations for this methodology.

During the course of the total syntheses of several natural products and potential biomimetic precursor substrates, we have needed to couple functionalized activated esters to gramine derivatives of various indole ring systems. Three literature methods can be used to form the desired carbon–carbon bond. First, heating of gramine **1** to temperatures greater than >120 °C leads to spontaneous formation of 3-methylene-3*H*-indole (**2**) via loss of the dimethyl amine (Scheme 1).[1] Trapping of **2** with nucleophiles such as a malonate enolate or cyanide generates the desired 3-substituted indole **3**. This procedure can result in good yields of the coupled product, but with the high temperatures employed may not be suitable for sensitive substrates. Alternatively, Somei[2] and Kametani[3] independently reported that the temperature can be reduced to ~90 °C by the addition of 0.4 equiv of tri-*n*-butylphosphine. The precise role of the phosphine catalyst is still unclear at this time. However, one mechanistic hypothesis is that it acts as a nucleophilic catalyst forming a highly reactive phosphonium salt, which is more susceptible to the elimination and formation of **2**. As a milder alternative to the thermal conditions, the indole nitrogen of gramine **1** can be protected as the corresponding *N*-silyl gramine **4**.[4] Exposure of **4** to MeI or Me_2SO_4 generates a quaternary ammonium salt, which is readily eliminated in the presence of TBAF to generate **2**, which is trapped as before to yield **3**. These reaction conditions are quite general for a variety of substrates, but the use of a fluoride source to generate intermediate **2** makes it incompatible with substrates that require silyl protecting groups elsewhere in the molecule.



Scheme 1. Two methods for the coupling of gramines to activated esters.

Previously, our laboratory has successfully employed the conditions developed by Somei and Kametani for the preparation of substituted indole derivatives utilized in the synthesis of brevianamides and paraherquamides.[5]

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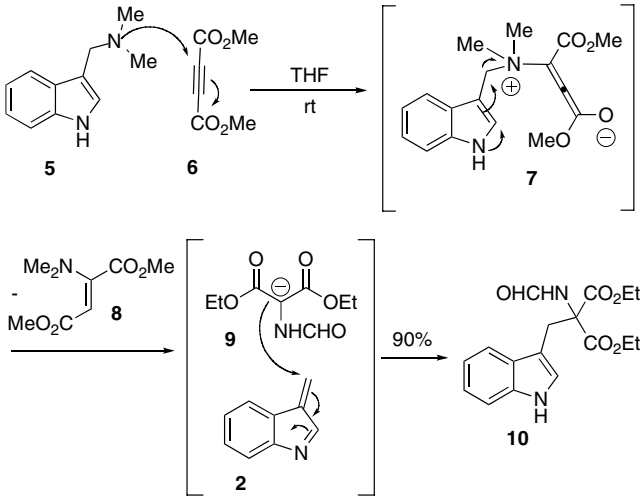
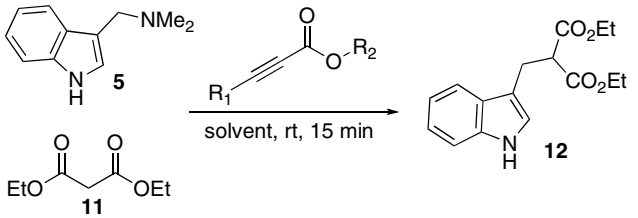
Unfortunately, as our malonate and indole substrates have become more complex the yields for this condensation reaction can be quite variable and range from good (~70%) to poor (~30%). As a result, we have examined alternative conditions for this key bond-forming reaction and were drawn to a report by Sainsbury, who demonstrated the facile coupling of gramine and an activated ester at room temperature using activated acetylenes.[6] The activation of gramine **5** occurs via conjugate addition on dimethyl acetylenedicarboxylate (DMAD, **6**) generating zwitterion **7** (Scheme 2). The loss of ammonium species via elimination leads to the formation of enamine **8** and reactive 3-methylene-3*H*-indole (**2**). Trapping of the anion of *N*-formyl diethylaminomalonate (**9**) generates the desired product **10** in 90% yield after only 15 min. With only two examples of this reaction reported by Sainsbury, we have performed a series of experiments to explore the scope and limitations of these conditions in effort to better understand how this mild coupling method can be applied to natural product synthesis.[7]

In the original report by Sainsbury, the only activated acetylene employed was DMAD. As such, we commenced our experiments by screening a panel of commercially available activated acetylenes (Table 1).[8,9] Due to the speed of the reaction, two important details were quickly ascertained from the coupling of gramine (**5**) to diethylmalonate (**11**) in THF at rt. First, acetylenes possessing a single carboxylate group (entries a–c) generated **12** in moderate to good yields (47–78%). Second, once the acetylene was di-substituted with a carboxylate group at one terminus and an alkyl or aryl group at the other, no reaction was observed between the malonate and the gramine (entries e–h). It is postulated that these results are observed due to the acetylene becoming: (1) more electron-rich and therefore less susceptible to conjugate addition (entries d–f); and (2) more sterically encumbered (entries g and h). This initial screening of reagents revealed that commercially available ethyl propiolate readily affords the alkylated malonate **12** in a good yield (entries i–l).



Scheme 2. DMAD mediated coupling of gramine to *N*-formyl diethylaminomalonate.

Table 1. Alkylation of gramine (**5**) with diethylmalonate (**11**) in the presence of commercially available activated actetylenes

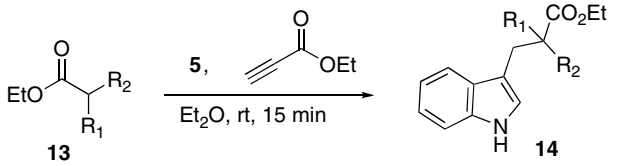


Entry	R_1	R_2	Solvent	Yield of **12** (%)
a	H	Et	THF	78
b	H	Me	THF	77
c	H	*tert*-Bu	THF	47
d	*n*-Propyl	Me	THF	0
e	Me	Et	THF	0
f	Et	Et	THF	0
g	Ph	Et	THF	0
h	Ph	Me	THF	0
i	H	Et	CH_3CN	85
j	H	Et	CH_2Cl_2	86
k	H	Et	MeOH	60
l	H	Et	Et_2O	90

With the reagent screen completed, we began to explore the influence of different solvents on this reaction. Our initial reagent screen was conducted in THF, the same solvent employed by Sainsbury. We have found that performing the coupling in different solvents can significantly influence the yield of this reaction. Switching from THF to CH_3CN (entry i) or CH_2Cl_2 (entry j) increased the yield from 78% to 85% and 86%, respectively. Interestingly, a protic solvent like MeOH (entry k) also generates the desired product, albeit in a depressed 60% yield. However, Et_2O (entry l) proved to be the best solvent for this reaction resulting in 90% yield of the alkylated product **12** after 15 min at room temperature.

Based on these preliminary results, we alkylated a series of malonate derivatives **13** with gramine (**5**) in the presence of ethyl propiolate in less than 20 min (Table 2).[10]

Table 2. Coupling of gramine (**5**) with different activated esters **13** in the presence of ethyl propiolate

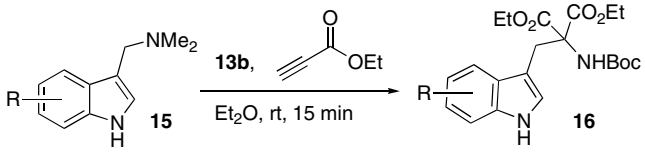


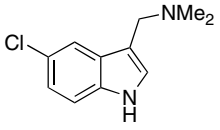
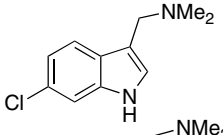
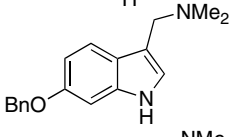
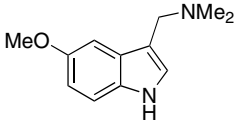
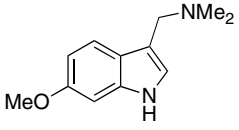
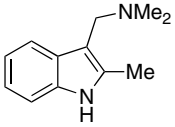
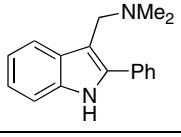
Entry	Ester derivatives	Yield of **14** (%)
a	$R_1 = CN$, $R_2 = H$	67
b	$R_1 = CO_2Et$, $R_2 = NHBoc$	65
c	$R_1 = Ac$, $R_2 = H$	83
d	$R_1 = NO_2$, $R_2 = H$	65[a]
e	$R_1 = N = CPh_2$, $R_2 = H$	41
f	$R_1 = NHBoc$, $R_2 = H$	0
g	$R_1 = N_3$, $R_2 = H$	0

[a] Due to solubility problems, this coupling was conducted in CH_2Cl_2.

As a result, several trends were observed. First, activated esters **13** needed to have a pK_a lower than 16 in DMSO for good to excellent yields of the alkylated product (entries a–d). Second, alkylations of activated esters with low pK_a's like ethyl cyanomalonte (entry a) and ethyl nitroacetate (entry d) were often accompanied by small amounts of dialkylated products (<20%), thereby depressing the yield of monoalkylated product **14**. Malonates that contain bulky substituents like *N*-Boc diethylaminomalonate (entry b) also gave lower yields (65%) presumably due to increased steric interactions. Interestingly, coupling of the benzophenone imine of glycine (entry e) did afford product, but in a disappointing 41% yield. We believe this example represents the upper limit of the pK_a range required for this methodology (pK_a = 19.5). This is further confirmed by the failed alkylation of *N*-Boc ethyl glycine (entry f) and ethyl azidoacetate (entry g), both of which have pK_a's greater than 20.

Table 3. Coupling of *N*-Boc diethylaminomalonate (**13b**) with various indole derivatives of gramine **15** in the presence of ethyl propiolate



Entry	Gramine	Yield of **16** (%)
a		54
b		44
c		65
d		42
e		53
f		61
g		62

In addition to the scope of the activated ester, we explored the influence of indole ring system of the gramine and its ability to couple to the activated ester in the presence of ethyl propiolate. Commercially available indoles were converted to their respective gramines **15** using the known literature procedures (CH_2O, Me_2NH, AcOH, rt) in good to excellent yields. Exposure of gramine **15** to *N*-Boc diethylaminomalonate (**13b**) in the presence of ethyl propiolate in Et_2O readily generated the desired tryptophan derivatives **16** (Table 3). Both electron-poor and electron-rich indole ring systems couple under these conditions in good yields. In addition, sterically demanding C2-substituted gramines (Table 3, entry g) readily afford the tryptophan derivative **16g** in 62% yield. The coupled products **16** can readily be converted to the racemic tryptophan derivatives using the known literature methods.[11]

In conclusion, we have studied the scope and limitations on the mild coupling of activated esters to gramines using the inexpensive reagent ethyl propiolate. In comparison to similar reactions, this carbon–carbon bond-forming event takes place at room temperature in moderate to good yields in several common organic solvents using many different activated esters and gramines. Finally, we are attempting to develop an asymmetric variant of this coupling reaction for the enantioselective synthesis of tryptophans analogues readily derived from various gramines.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and NMR spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.016.

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9. All reagents were used without further purification from commercially sources. For detailed experimental procedures, see Supplementary data.
10. *General procedure:* The gramine (1.1 equiv) is suspended in Et_2O (0.2 M). The activated ester (1.0 equiv) is added in a single portion followed by ethyl propiolate (1.1 equiv) via syringe. The reaction mixture is stirred until no more starting material is visible by TLC (~20 min). The reaction mixture is poured into a separatory funnel containing EtOAc. The organic solution is washed with 1 N HCl, water and brine. The organic layer is dried over Na_2SO_4 and the volatile organics removed under reduced pressure. The crude product is purified by flash silica gel chromatography.
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