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A simple one-step protocol for the olefination of vinylogous formamides

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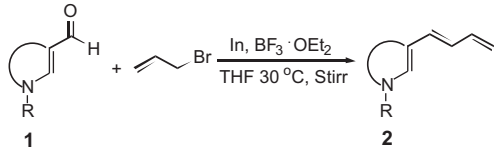
Abstract—Vinylogous formamides—5-formyluracils and 4-formylpyrazoles-undergo smooth olefination in THF in the presence of indium metal (0.8 equiv) and $BF_3{\cdot}OEt_2$ (1 equiv) and allyl bromide (1 equiv) to provide the respective diene-substituted heterocycles in a single step.

Conjugated 1,3-dienes, being constituents of Diels–Alder and related reactions, are broadly useful intermediates in organic synthesis.[1] General methods for the synthesis of 1,3-dienes include elimination of allylic alcohols/halides, reductive elimination of dihalogenated compounds and transition metal coupling reactions of vinylic compounds etc.[2] The more versatile Peterson olefination approach involves the addition of γ-silyl-substituted allylmetal reagents viz. silylated allylboronates,[3] allyltitanates,[4] allylzirconiums[5] to an aldehyde followed by eliminative desilylation, but it is plagued by the necessity to use expensive reagents and multistep sequences. Therefore, the development of an economical and straightforward synthetic methodology for such dienes is highly desirable.

In recent years, indium has found widespread applications in allylation of a variety of functional groups including carbonyl, imine, epoxide and olefin.[6] In general, in indium mediated allylation, the homoallylic indium alkoxide intermediate on hydrolysis yields a homoallylic alcohol as the [1,2]-addition product. Recently, the electronic contribution of C=C bond has been used, in conjugated aldehydes for synthesis of cyclopropanes,[7] and more conveniently in heterocyclic aldehydes for the synthesis of 3-(hepta-1,6-dien-4-yl)-indoles and pyrroles,[8] bis-indolyl alkanes and indolyl heterocyclic alkanes.[9] In all these cases, nucleophilic substitution at the indium alkoxide carbon is the key step in the in situ transformations of the homoallylic alcohol. However, there are many examples where nucleophilic substitution and elimination reactions proceed side by side in competition and variations in the leaving groups, nature of base and solvent can readily favour one of these two reaction processes. Here we report an indium–$BF_3{\cdot}OEt_2$ mediated one-step protocol where 1,2-addition products of vinylogous formamides undergo in situ olefination through deoxygenative elimination to provide 1,3-butadiene-substituted aza-heterocycles (Scheme 1).[10]

A solution of **1a**, allyl bromide and indium metal (1:1:0.8) in dry THF in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ on stirring at 30 ± 1 °C (Scheme 1)[11] gave a thick liquid (72%) M^+ m/z 192 (M^+). The ^1H NMR spectrum of this product showed the presence of well-defined signals with appropriate multiplicities for each hydrogen. Three ^1H doublets at δ 5.13 ($J = 10$ Hz), 5.30 ($J = 16.8$ Hz) and 6.27 ($J = 15.8$ Hz), a double triplet at δ 6.40 ($J_1 = 10.4$ Hz, $J_2 = 16.8$ Hz) and a double doublet at δ 7.07 ($J_1 = 10.4$ Hz, $J_2 = 15.8$ Hz) along with N–Me and 6H signals confirm the structure **2a** for this compound.



1 2

Scheme 1.

Keywords: Indium; Olefination; Dienes; Vinylogous formamides; Stereoselective.

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The reaction of **1a** with indium and allyl bromide in THF–H_2O or in dry THF under Barbier type conditions provided only the 1,2-addition product 5-[1-(1-hydroxybut-3-enyl)] uracil. Also, on using $SnCl_4$ or $Yb(OTf)_3$ as the Lewis acids, again only the 1,2-addition product was obtained and the formation of diene was not observed. Therefore, stirring of **1a** in dry THF with indium, allyl bromide and $BF_3{\cdot}OEt_2$ at 301 °C constitutes the optimal conditions for the olefination.

In order to investigate the scope of this protocol in the olefination of other heterocyclic vinylogous formamides, the olefination of a number of uracil and pyrazole derivatives possessing vinylogous formamide units, under the optimized conditions was investigated (Table 1). The results clearly reveal the scope and the generality of the protocol with respect to variously substituted vinylogous formamides. The presence of methyl (entry **b**), dialkylamino (entry **c** and **d**) and alkylarylamino (entry **e**) at C-6 of uracil and the substituents on the 1-, 3- and 5-positions of pyrazole do not effect the olefination process. However, aromatic/aliphatic aldehydes under these conditions provided only homoallylic alcohol.

These reactions proceed with high geometric selectivities as the formation of only one diene geometrical isomer was observed by ^1H NMR spectra. In the cases of **2a**–**e**, all the diene systems show well-defined multiplicities. In the case of **2a**, the decoupling of doublet at δ 5.13 (H-4″) or doublet at δ 5.30 (H-4′) converted dt at δ 6.40 (H-3′) to a double doublet and decoupling of doublet at δ 6.27 (H-1′) converted dd at δ 7.07 (H-2′) to doublet. The decoupling of dt at δ 6.40 (H-3′) converted the doublets at δ 5.13 (H-4″) and 5.30 (H-4′) to singlets and dd at δ 7.07 (H-2′) to doublet. The decoupling of dd at δ 7.07 (H-2′) converted doublet at δ 6.27 (H1′) to singlet and dt at δ 6.40 (H-3′) to a triplet. These decoupling experiments unambiguously assign the signals to diene protons as shown in **2a**. The coupling constants between 10 and 17 Hz assign all *trans* structure to the diene. The most downfield shift of H-2′ dd (δ 7.07) points towards the proximity of H-2′ and the carbonyl oxygen of uracil. In NOE experiments, the enhancement of H-1′ and H-4″ signals on irradiation of the H-3′ signal convincingly settles the geometry of the diene system. Similarly, in the case of the other diene-substituted uracils, the geometry was defined by ^1H decoupling and NOE experiments. However, in the case of the pyrazole derivatives, the terminal C–H signal appeared as two doublets with $J = 10.4$ and 15.8 Hz but the other diene proton signals appeared as a multiplet and so relative geometry could not be defined.

To broaden the scope of this olefination reaction further for the synthesis of more substituted olefins, the reactions of **1c** with substituted allyl bromides were performed. Compound **1c** on reaction with crotyl bromide provided the diene-substituted uracil **3**, which existed as

Table 1. Synthesis of 1,3-diene-substituted azaheterocycles **2**

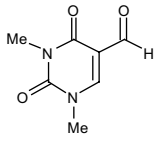
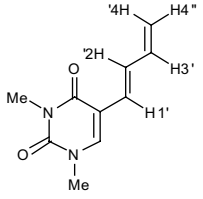
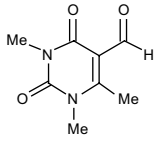
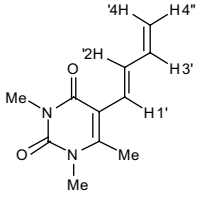
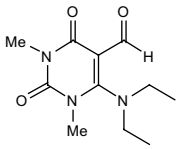
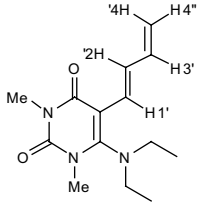
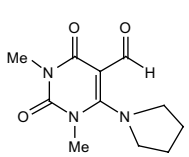
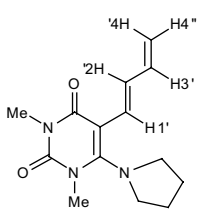
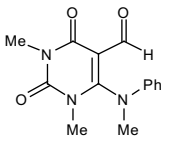
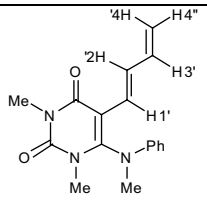
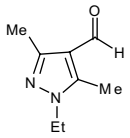
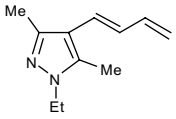
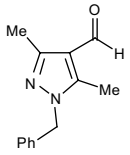
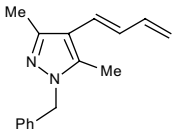
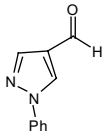
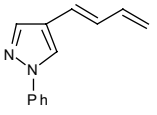
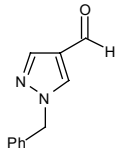
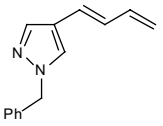
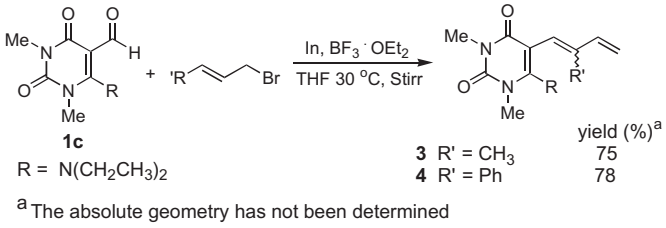
Entry	Formamide **1**	Diene **2**	Yield (%)[a]	M^+ (m/z)
a			72	192
b			74	206
c			72	263
d			68	261

Table 1 (*continued*)

Entry	Formamide **1**	Diene **2**	Yield (%)[a]	M^+ (m/z)
e			74	297
f			78	176
g			82	238
h			63	196
i			69	210

[a] Isolated yields.



Scheme 2.

a 2:1 mixture of two configurational isomers. Similarly, **1c** with cinnamyl bromide gave **4** as a 4:1 mixture of two configurational isomers (Scheme 2).

In conclusion, the milder conditions, use of unsophisticated cheaper reagents, high stereoselectivities and cleaner reaction profiles associated with the present one-step protocol makes it an attractive method for the olefination of vinylogous formamides **1** to provide diene-substituted azaheterocycles.

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11. **General procedure:** A suspension of indium metal (0.8 mmol), allyl bromide (1 mmol), vinylogous formamide (1 mmol) and $BF_3{\cdot}OEt_2$ in dry THF (5 mL) was stirred at 30±1 °C until the completion of reaction (TLC). The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated to yield the crude products, which were purified by silica gel column chromatography. The spectroscopic data for some representative compounds is given: compound **2a** (72%), thick liquid, M^+ m/z 192; ^{1}H NMR ($CDCl_3$): δ 3.37 (s, 3H, N–CH_3), 3.43 (s, 3H, N–CH_3), 5.13 (d, $J = 10$ Hz, 1H, H-4′), 5.30 (d, $J = 16.8$ Hz, 1H, H-4″), 6.27 (d, $J = 15.8$ Hz, 1H, H-1′), 6.40 (dt, $J_1 = 10.4$ Hz, $J_2 = 16.8$ Hz, 1H, H-3′), 7.07 (dd, $J_1 = 10.4$ Hz, $J_2 = 15.8$ Hz, 1H, H-2′), 7.22 (s, 1H, 6-H); ^{13}C (normal/DEPT) NMR: δ 28.07 (+ve, CH_3), 36.92 (+ve, CH_3), 111.09 (ab, C-5), 117.67 (−ve, =CH_2), 123.69 (+ve, CH), 130.39 (+ve, CH), 137.20 (+ve, CH), 138.95 (+ve, CH), 150.86 (ab, C=O), 161.92 (ab, C=O). Compound **2c** (72%), thick yellow liquid, M^+ m/z 263 (M^+); ^{1}H NMR ($CDCl_3$): δ 1.17 (t, $J = 7.0$ Hz, 6H, $2 \times CH_3$), 3.18 (q, $J = 7.0$ Hz, 4H, $2 \times CH_2$), 3.36 (s, 3H, N–CH_3), 3.38 (s, 3H, N–CH_3), 5.08 (d, $J = 10.6$ Hz, 1H, H-4′), 5.29 (d, $J = 16.8$ Hz, 1H, H-4″), 6.09 (d, $J = 15.6$ Hz, 1H, H-2′) 6.38 (dt, $J_1 = 16.8$ Hz, $J_2 = 10.6$ Hz, 1H, H-3′) 7.36 (dd, $J_1 = 15.6$ Hz, $J_2 = 10.6$ Hz, 1H, H-2′). ^{13}C (normal/DEPT): δ 28.82 (+ve, CH_3), 33.47 (+ve, CH_3), 33.47 (+ve, CH_3), 46.65 (−ve, CH_2), 104.85 (ab, Ura C-5), 117.10 (−ve, CH_2), 124.86 (+ve, CH), 132.45 (+ve, CH), 139.07 (+ve, CH), 152.40 (ab, C=O), 154.48 (ab, C-6), 163.05 (ab, C=O).