Tetrahedron 65 (2009) 3197–3201

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Conjugate allylation reactions of alkylidene malononitriles mediated by NHC-ligated palladium catalysts

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ARTICLE INFO

Article history:
Received 18 September 2008
Received in revised form 18 October 2008
Accepted 21 October 2008
Available online 25 October 2008

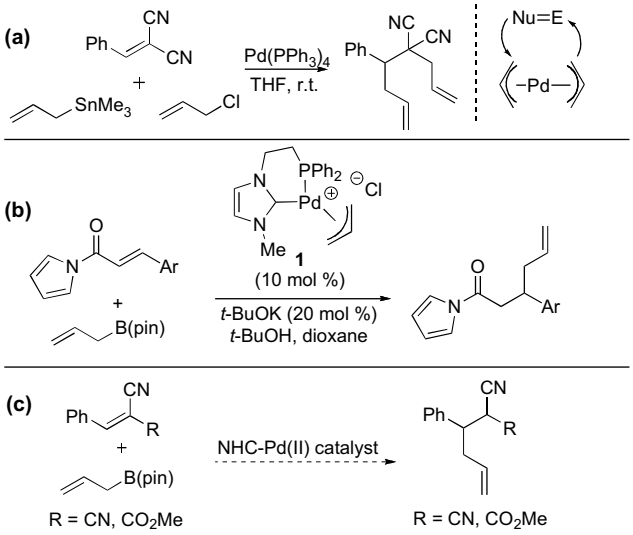
ABSTRACT

Conjugate allylation of malononitriles is reported using catalytic *N*-heterocyclic carbene-ligated palladium complexes. This conjugate allylation reaction yields a variety of monoallylated products. These results contrast the bis-allylation of malononitriles using other palladium-based catalysts. This reaction tolerates a wide variety of functional groups including aryl groups, heteroaromatics, and aliphatic substituents to provide the desired products in good to excellent yields. Derivatization of the monoallylation products to form a triamino pyrimidine is demonstrated.

1. Introduction

The development of conjugate addition methodologies that allow for the mild and efficient construction of a C–C bond presents an ongoing challenge in organic synthesis. Previous methods for conjugate additions have utilized aryl- or alkylhalides to form organocopper, organozinc, and organomagnesium reagents to obtain the desired 1,4-addition products.[1] While these methods have proven useful, relatively few methods for the conjugate addition of allylic nucleophiles have been reported.[2,3] In 2007, Morken and co-workers reported the first enantioselective, Ni- and Pd-catalyzed conjugate addition of allylboranes to styryl-activated enones.[4] Recently, Snapper and co-workers have shown the use of chiral copper catalysts in their report of an enantioselective Hosomi–Sakurai conjugate allylation of cyclic ketoesters.[5] These reports were significant advances in the area of conjugate allylation and highlight the limited substrate scope of catalytic conjugate allylation reactions.

Nucleophilic allylpalladium complexes have emerged as useful catalysts for allylation reactions of imines and aldehydes, as well as for bis-allylation reactions of malononitriles.[6] Yamamoto reported the amphiphilic nature of bis-π-allylpalladium complexes when reacting with malononitriles (Scheme 1a).[7] These reactions are thought to initiate by attack of a nucleophilic allyl moiety on the malononitrile. Subsequent attack on the resultant electrophilic allylpalladium complex produces bis-allylated products. The catalytic bis-π-allylpalladium complex is regenerated by reaction with allylbromide and tributylallylstannane. In all reported reactions of malononitriles catalyzed by bis-π-allylpalladium complexes monoallylated products were not obtained.[7b] Though the bis-allylation is well known, transition metal-catalyzed reactions that afford monoallylation products of malononitriles have yet to be reported.



Scheme 1.

Recently, our laboratories have expanded the conjugate allylation substrate scope to include α,β-unsaturated *N*-acylpyrroles through a palladium-catalyzed reaction (Scheme 1b).[8] Key to the success of this conjugate addition was the *N*-heterocyclic carbene (NHC)-ligated palladium complex (**1**) that renders the allyl moiety nucleophilic. NHC-ligated palladium complexes have shown utility

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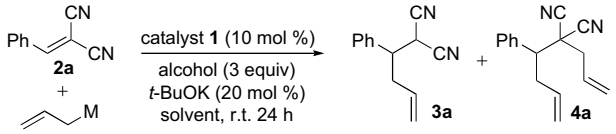
doi:10.1016/j.tet.2008.10.061

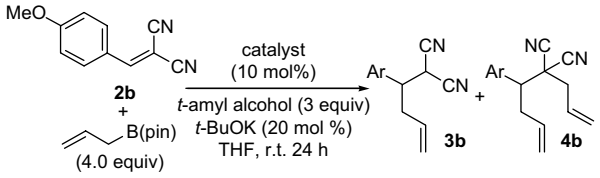
Table 1
Monoallyation of malononitrile **2a** utilizing Pd(II) catalysis



Entry	M	AllylM (equiv)	Alcohol	Solvent	Combined yield[a,b] (%)
1	B(pin)	2.3	*tert*-Amyl alcohol	THF	63
2	B(pin)	2.3	*tert*-Amyl alcohol	DCM	30
3	B(pin)	5.0	*tert*-amyl alcohol	THF	80
4	B(pin)	5.0	*t*-BuOH	THF	60
5	B(pin)	5.0	*t*-BuOH	Dioxane	36
6	B(pin)	5.0	*tert*-Amyl alcohol	Dioxane	64
7	BF_3K	2.0[c]	*tert*-Amyl alcohol	THF	0
8	BF_3K	2.0	*tert*-Amyl alcohol	THF	0

[a] Combined isolated yields of products **3a** and **4a** after column chromatography.
[b] Isolated as a 5:1 to 7:1 ratio of **3a**/**4a**.
[c] No base was added.

Table 2
Catalyst screen



Entry	Catalyst	Ratio **3b**/**4b**[a]	Combined yield[b] (%)
1	**1**	2.8:1	90
2	**5**	2:1	87
3	**6**	4:1	84
4	**7**	6.7:1	90
5	$Pd(OAc)_2$	2:1	31
6	$[Pd(allyl)Cl]_2$	NA	<5

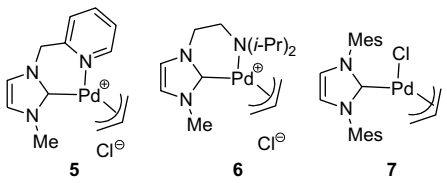
[a] Ratio determined by ^1H NMR analysis of the unpurified reaction mixture.
[b] Combined isolated yield of **3b** and **4b** after column chromatography.

in various cross-coupling reactions[9] as well as in the allylation of aldehydes.[10] Based on the success of these transformations, and the limitations of the previously mentioned conjugate allylation methodologies we began to investigate the ability of NHC–Pd complexes to catalyze the conjugate allylation of malononitriles (Scheme 1c).

2. Results and discussion

Our hypothesis centered on the ability of NHC-ligated palladium complexes to catalyze the allylation of various malononitrile substrates with allylboronic ester [allylB(pin)]. Our initial studies began by employing palladium complex **1** to mediate the conjugate allylation of malononitrile **2**. Effects of various solvents, alcohols, and allyl sources were determined. A control experiment confirmed that in the absence of a palladium catalyst no reaction was observed with complete recovery of starting material. The bidentate NHC–phosphine ligated palladium complex **1** catalyzed the formation of **3a** in the presence of allylB(pin), *t*-BuOK, and *tert*-amyl alcohol (Table 1 entry 1). This reaction provided a 6:1 ratio of mono- to bis-allylated products (**3a** and **4a**, respectively). The remaining material was attributed to unreacted starting material **2a**. Increasing the number of equivalents of allylB(pin) to 5.0 and using THF as the solvent provided an 80% yield of the desired allylated products (entry 3).[11] Changing solvents as well as using other alcohol sources did not increase the overall yields of the reaction. Switching to potassium allyltrifluoroborate as the transmetallating agent provided no desired product and quantitative recovery of starting material (entries 7 and 8).

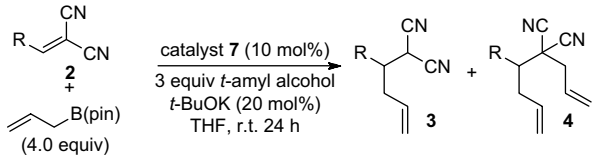
We began to explore the generality of this Pd(II)-catalyzed conjugate allylation of malononitriles. In our initial screens we observed that the overall reactivity for substrates with electron-donating groups was very good; however, these substrates were more susceptible to bis-allylation. For example, methoxy-substituted malononitrile (**2b**) provided a 2.8:1 ratio of **3b** to **4b** in 90% combined yield (Table 2, entry 1). We examined other NHC-ligated palladium complexes to reduce the amounts of bis-allylation byproduct (Table 2). These reactions were conducted under the same conditions as reported in Table 1; however, fewer equivalents of allylB(pin) were required to obtain complete conversion of substrate **2b**. Other bidentate NHC-ligated complexes provided similar results: NHC–pyridine complex **5** resulted in a 2:1 ratio of **3b**/**4b** and NHC–amine complex **6** led to a 4:1 ratio of the mono- to bis-allylated products. The commercially available monodentate NHC complex **7** provided the best results, generating a 6.7:1 ratio of **3b**/**4b**. To ensure the NHC ligand was necessary other palladium complexes were examined (entries 5 and 6). $Pd(OAc)_2$ afforded a 2:1 mixture of the desired products in a 31% overall yield, along with a 50% yield of unreacted starting material. Employing Yamamoto's catalyst, allylpalladium chloride dimer provided no desired product.

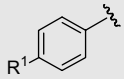
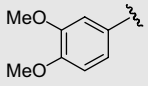
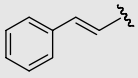
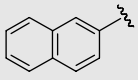
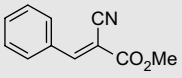
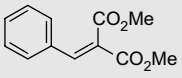
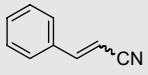


A variety of malononitrile substrates were subjected to the optimized conjugate addition conditions using catalyst **7** (Table 3). Reactions of malononitriles substituted with phenyl and electron-donating aryl groups afforded products in good to excellent yields and gave good to excellent selectivity for the monoallylated species (entries 1–4). It should be noted that in all cases the mono- and bis-allylated species were easily separable by column chromatography. Haloarenes such as **2d** also reacted smoothly to provide **3d** in 77% yield (entry 5). Substrates containing electron-withdrawing aryl groups did react under the given conditions, but gave incomplete conversion and lower yields. Substrate **2e**, bearing two methoxy groups, gave the highest amount of bis-allylation of any substrate examined, with a 4.4:1 ratio obtained in 91% combined yield (entry 6). The cinnamyl derivative (**2f**) reacted regioselectively to provide the product of 1,4-addition over the 1,6-addition, albeit in a slightly lower yield (entry 7). Substrates bearing other aromatic and aliphatic substituents such as furyl, pyridyl, napthyl, and cyclohexyl were also viable partners for this conjugate allylation generating the desired products in excellent yields (entries 8–11). Lastly, the conjugate addition to the cyanoacetate derivative **8** provided monoallylated product in 82% yield as a 2:1 ratio of diastereomers (entry 12). Efforts to allylate malonate derivatives were unsuccessful providing <5% yield of the desired product and unreacted starting material (entry 13). Additionally, when cinnamonitrile was subjected to the reaction conditions no desired product was obtained (entry 14).

The monoallylated malononitriles products can be diversified to rapidly construct functionalized building blocks for further synthetic manipulations. For example, straightforward α-alkylation, reduction of the nitriles,[12] or formation of β-amino acids when using cyanoacetate substrates[13] is possible. Furthermore, various heterocycles can be rapidly constructed by reacting malononitriles with ureas, thioureas, and hydrazine.[14] These reactions require an

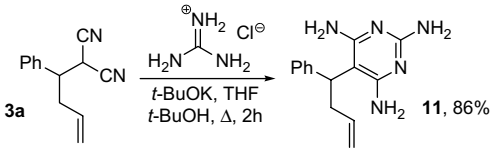
Table 3
Conjugate allylation of malononitriles



Entry	R	Substrate	Ratio **3**/**4**[a]	Yield **3**[b] (%)
1		**2a**, R^1=H	>20:1	63
2		**2a**, R^1=H	7:1	70[c]
3		**2b**, R^1=OMe	6.7:1	79
4		**2c**, R^1=Me	7:1	81
5		**2d**, R^1=Br	>20:1	73
6		**2e**	4.4:1	74
7		**2f**	17:1	54
8		**2g**	5:1	79
9		**2h**	>20:1	82[c]
10		**2i**	>20:1	70
11		**2j**	10:1	82
12		**8**	>20:1	82[d]
13		**9**	NA	<5
14		**10**	NA	<5

[a] Ratio determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.
[b] Isolated yield of **3** after column chromatography.
[c] Catalyst **1** (10 mol %) was employed.
[d] Isolated as a 2:1 mixture of diastereomers.

acidic α-hydrogen and are therefore not possible with products of bis-allylation. To demonstrate the potential utility of the reaction products for the preparation of bioactive compounds, we prepared triamino pyrimidine **11** from monallylated **3a** using guanidine[15] in 86% yield (Eq. 1).



(1)

3. Conclusions

We report the palladium-catalyzed conjugate allylation of malononitriles. Use of the NHC-ligated catalyst is critical to achieve a monoallylation reaction with malononitriles. The scope of this reaction includes alkylidene malononitriles substituted with electron-rich aryl, pyridyl, furyl, aliphatic, and vinyl groups and cyanoacetates. Overall, this report has expanded the substrates amenable to conjugate allylation and shown the utility of NHC–Pd catalysts to mediate a single allylation event with various malononitriles. Continued study of the mechanism, functional group tolerance of the reaction, as well as development of enantio- and diastereoselective variants of this conjugate allylation process are ongoing in our laboratories.

4. Experimental

4.1. General procedure

All reactions were carried out under an atmosphere of N_2. All glassware was either oven or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were degassed with argon and then passed through two 4×36 inch columns of anhydrous neutral A-2 alumina (8×14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 h) to remove H_2O. All other solvents utilized were purchased 'anhydrous' commercially, or purified as described (vide infra). Molarities of organolithium and organomagnesium reagents were determined by titration with menthol/bipyridine.[16] ^{1}H NMR spectra were recorded on Bruker GN-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C), CRYO-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C) or DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. Proton chemical shifts are reported in parts per million (δ) relative to the solvent resonance ($CDCl_3$, δ 7.27) Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet of triplets (tt), quartet (q), multiplet (m), apparent doublet (ad), broad doublet (br d) and broad multiplet (br m)]), coupling constants [Hz], integration. Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.23 ppm). Unless otherwise indicated, NMR data were collected at 25 °C. Infrared spectra were obtained on a Mattson Instruments *Galaxy 5000* spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F_{254} precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with an UV lamp and/or staining with $KMnO_4$, ceric ammonium molybdate (CAM), or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60A (170–400 mesh) from Fisher Scientific. Allylboronic acid pinacol ester was purchased from Frontier Scientific, Inc. and was distilled through a 15 cm Vigreux fractionating column connected to a short-path distillation head (95 °C, 17 Torr) to remove $B(OH)_3$. Potassium *tert*-butoxide was purchased from Alfa Aesar, stored in a glovebox, and used as received. All malononitrile alkylidenes were prepared according to the reported literature procedures.[17] Palladium complexes **1**, **8**, **9**, and **10** were prepared by modification of the synthetic sequence we have previously reported.[18] High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

4.2. General procedure for allylation of malononitriles (Table 3)

4.2.1. 2-(1-(4-Methoxyphenyl)but-3-enyl)malononitrile (*3b*)

To an oven-dried 8 mL scintillation vial with screw-top cap fitted with a silicon/Teflon septa and magnetic stir bar was added malononitrile **2b** (0.036 g, 0.20 mmol). Then 0.800 mL of anhydrous THF was added by syringe, followed by addition of allylboronic acid pinacol ester (0.153 mL, 0.800 mmol) and *tert*-amyl alcohol (0.066 mL, 0.6 mmol). Lastly, allylpalladium complex **7** (0.0096 g,

0.020 mmol) and potassium *tert*-butoxide (0.0045 g, 0.04 mmol) were added successively to the solution. The reaction mixture was stirred at 23 °C for 24 h. Purification was performed using silica gel chromatography (10:1 hexane/EtOAc) affording **3b** as a colorless oil (36 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (ad, J=7.5 Hz, 2H), 6.94 (ad, J=8.7 Hz, 2H), 5.67 (dddd, J=16.5, 14.1, 7.8, 6.2 Hz, 1H), 5.25 (dd, J=17.1, 1.3 Hz, 1H), 5.18 (ad, J=10.3 Hz, 1H), 3.99 (d, J=5.5 Hz, 1H), 3.83 (s, 3H), 3.26 (ddd, J=7.7, 7.6, 5.6 Hz, 1H), 2.79–2.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.2, 133.4, 129.3, 128.4, 120.0, 114.8, 112.3, 111.8, 55.5, 45.5, 36.7, 29.5; IR (thin film, cm^{-1}) 298, 2838, 2254, 1612, 1515; HRMS (TOF MS ES$^+$) m/z calculated for $C_{14}H_{14}N_2O$ 249.1004, $[M+Na]^+$ found 249.1002; TLC R_f=0.2 (3:1 hexanes/EtOAc).

4.2.2. 2-(1-Phenylbut-3-enyl)malononitrile (**3a**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.25 (m, 5H), 5.70–5.60 (m, 1H), 5.23 (d, J=17.0 Hz, 1H), 5.17 (d, J=10.2 Hz, 1H), 4.01 (d, J=5.6 Hz, 1H), 3.29 (m, 1H), 2.75 (m, 2H). The spectral values obtained were consistent with those reported in the literature.[19]

4.2.3. 2-Allyl-2-(1-(4-methoxyphenyl)but-3-enyl) malononitrile (**3b**)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, J=9.3 Hz, 2H), 6.94 (d, J=7.0 Hz, 2H), 5.95–5.83 (m, 1H), 5.55–5.45 (m, 1H), 5.40 (dd, J=8.1, 0.6 Hz, 1H), 5.32 (dd, J=13.6, 0.9 Hz, 1H), 5.08 (dd, J=13.6, 1.2 Hz, 1H), 4.98 (dd, J=9.2, 1.0 Hz, 1H), 3.93 (s, 3H), 3.05 (dd, J=9.3, 3.2 Hz, 1H), 2.95–2.84 (m, 2H), 2.50 (dd, J=11.1, 5.9 Hz, 1H), 2.40 (dd, J=11.2, 5.7 Hz, 1H). Analytical data is consistent with the reported literature values.[20]

4.2.4. 2-(1-p-Tolylbut-3-enyl)malononitrile (**3c**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.16 (m, 4H), 5.68 (dddd, J=16.9 10.6, 7.6, 6.4 Hz, 1H), 5.25 (dd, J=17.1, 1.4 Hz, 1H), 5.18 (ad, J=10.3 Hz, 1H), 4.00 (d, J=5.7 Hz, 1H), 3.26 (ddd, J=7.7, 7.6, 5.7 Hz, 1H), 2.80–2.68 (m, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.1, 133.5, 133.4, 130.1, 128.0, 120.0, 112.2, 111.8, 45.8, 36.6, 29.3, 21.3; IR (thin film, cm^{-1}) 3081, 2921, 2254, 1643, 1515; HRMS (TOF MS ES$^+$) m/z calculated for $C_{14}H_{14}N_2$ 233.1055, $[M+Na]^+$ found 233.1055; TLC R_f=0.3 (3:1 hexanes/EtOAc).

4.2.5. 2-Allyl-2-(1-p-tolylbut-3-enyl)malononitrile (**4c**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.19 (m, 4H), 5.89 (dddd, J=16.9 10.6, 7.6, 6.4 Hz, 1H), 5.68 (dddd, J=16.9 10.6, 7.6, 6.4 Hz, 1H), 5.25 (dd, J=17.1, 1.4 Hz, 1H), 5.18 (ad, J=10.3 Hz, 1H), 4.00 (d, J=5.7 Hz, 1H), 3.26 (ddd, J=7.7, 7.6, 5.7 Hz, 1H), 2.80–2.68 (m, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.1, 133.8, 132.0, 130.0, 129.1, 129.0, 123.3, 118.6, 115.6, 114.7, 51.1, 43.5, 40.7, 36.4; IR (thin film, cm^{-1}) 3083, 2983, 2925, 2246, 1643; HRMS (TOF MS ES$^+$) m/z calculated for $C_{17}H_{18}N_2$ 273.1368, $[M+Na]^+$ found 273.1367; TLC R_f=0.4 (3:1 hexanes/EtOAc).

4.2.6. 2-(1-(4-Bromophenyl)but-3-enyl)malononitrile (**3d**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, J=8.5 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 5.66 (dddd, J=16.5, 10.5, 7.8, 6.4 Hz, 1H), 5.25 (dd, J=17.0, 1.4 Hz, 1H), 5.21 (dd, J=10.5, 1.3 Hz, 1H), 4.02 (d, J=5.5 Hz, 1H), 3.27 (ddd, J=7.6, 7.6, 5.6 Hz, 1H), 2.80–2.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.4, 132.8, 132.6, 129.8, 123.4, 120.5, 111.9, 111.4, 45.5, 36.5, 28.9; IR (thin film, cm^{-1}) 3081, 2904, 2360, 2256, 1643; TLC R_f=0.3 (3:1 hexanes/EtOAc).

4.2.7. 2-(1-(3,4-Dimethoxyphenyl)but-3-enyl)malononitrile (**3e**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (s, 2H), 6.86 (s, 1H), 5.73–5.64 (m, 1H), 5.26 (d, J=17.1 Hz, 1H), 5.19 (d, J=10.3 Hz, 1H), 4.01 (d, J=5.3 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.25 (ddd, J=7.7, 7.6, 5.4 Hz, 1H), 2.74 (at, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.7, 149.5, 133.4, 128.9, 120.5, 120.1, 112.3, 111.8, 111.6, 111.0, 56.2, 56.1, 45.9, 36.7, 29.4; IR (thin film, cm^{-1}) 3074, 3004, 2904, 2279, 1606, 1517; HRMS (TOF MS ES$^+$) m/z calculated for $C_{15}H_{16}N_2O_2$ 279.1110, $[M+Na]^+$ found 279.1115; TLC R_f=0.2 (3:1 hexanes/EtOAc).

4.2.8. 2-Allyl-2-(1-(3,4-dimethoxyphenyl)but-3-enyl)-malononitrile (**4e**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92–6.84 (m, 3H), 5.94–5.85 (m, 1H), 5.56–5.47 (m, 1H), 5.41 (ad, J=9.9 Hz, 1H), 5.41 (ad, J=16.8 Hz, 1H), 5.10 (ad, J=17.0 Hz, 1H), 5.00 (ad, J=10.0 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.03 (dd, J=11.6, 4.0 Hz, 1H), 2.92–2.81 (m, 2H), 2.50 (dd, J=14.1, 7.3 Hz, 1H), 2.40 (dd, J=13.9, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.4, 149.4, 133.6, 128.9, 127.2, 123.1, 121.9, 118.4, 115.5, 114.6, 111.2, 111.2, 56.0, 55.9, 51.0, 43.3, 40.5, 36.3; IR (thin film, cm^{-1}) 3083, 3004, 2838, 2246, 1643, 1517; HRMS (TOF MS APCI$^+$) m/z calculated for $C_{18}H_{20}N_2O_2$ 319.1422, $[M+Na]^+$ found 319.1419; TLC R_f=0.3 (3:1 hexane/EtOAc).

4.2.9. (E)-2-(1-Phenylhexa-1,5-dien-3-yl)malononitrile (**3f**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J=7.3 Hz, 2H), 7.36 (dd, J=7.8, 7.1 Hz, 2H), 7.32 (d, J=7.2 Hz, 1H), 6.71 (d, J=15.8 Hz, 1H), 6.10 (dd, J=15.8, 8.9 Hz, 1H), 5.81–5.71 (m, 1H), 5.28 (ad, J=17.0 Hz, 1H), 5.24 (d, J=10.1 Hz, 1H), 3.90 (d, J=4.9 Hz, 1H), 2.98–2.90 (m, 1H), 2.60–2.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.3, 135.7, 132.9, 128.9, 128.8, 127.0, 124.2, 112.2, 111.4, 44.3, 36.8, 27.9; IR (thin film, cm^{-1}) 3083, 2908, 2254, 1643, 1494; HRMS (TOF MS ES$^+$) m/z calculated for $C_{15}H_{14}N_2$ 245.1055, $[M+Na]^+$ found 245.1054; TLC R_f=0.3 (3:1 hexanes/EtOAc).

4.2.10. 2-(1-(Furan-2-yl)but-3-enyl)malononitrile (**3g**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (t, J=1.4 Hz, 1H), 6.40 (d, J=1.5 Hz, 2H), 5.72 (dddd, J=16.9, 9.4, 7.7, 6.5 Hz, 1H), 5.28 (dd, J=17.1, 1.3 Hz, 1H), 5.22 (dd, J=10.1, 1.1 Hz, 1H), 4.08 (d, J=5.9 Hz, 1H), 3.49 (ddd, J=7.3, 7.3, 1.0 Hz, 1H), 2.80–2.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.7, 143.5, 132.6, 120.5, 111.7, 111.4, 110.9, 109.4, 40.2, 35.3, 27.4; IR (thin film, cm^{-1}) 3083, 2921, 2248, 1642; TLC R_f=0.6 (3:1 hexanes/EtOAc).

4.2.11. 2-Allyl-2-(1-(furan-2-yl)but-3-enyl)malononitrile (**4g**)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (t, J=1.3 Hz, 1H), 6.40 (d, J=1.4 Hz, 2H), 5.90 (dddd, J=17.3, 10.3, 7.2, 7.2 Hz, 1H), 5.60 (dddd, J=16.9, 10.2, 6.8, 6.8 Hz, 1H), 5.43 (dd, J=10.2, 1.0 Hz, 1H), 5.38 (dd, J=16.8, 1.2 Hz, 1H), 5.13 (ddd, J=17.0, 2.8, 1.4 Hz, 1H), 5.06 (ddd, J=10.2, 2.5, 1.1 Hz, 1H), 3.31 (dd, J=9.9, 5.7 Hz, 1H), 2.90–2.80 (m, 2H), 2.59–2.44 (m, 2H); Analytical data is consistent with the reported literature values.[20]

4.2.12. 2-(1-(Pyridin-3-yl)but-3-enyl)malononitrile (**3h**)

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.67 (d, J=4.0 Hz, 1H), 8.62 (s, 1H), 7.74 (ad, J=7.82 Hz, 1H), 7.39 (dd, J=8.1, 4.9 Hz, 1H), 5.71–5.62 (m, 1H), 5.28 (ad, J=17.0 Hz, 1H), 5.23 (ad, J=10.0 Hz, 1H), 4.09 (d, J=5.4 Hz, 1H), 3.36 (ddd, J=7.7, 7.6, 5.6 Hz, 1H), 2.84–2.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.7, 149.9, 135.4, 132.4, 132.2, 124.2, 121.0, 111.7, 111.2, 43.7, 36.31, 29.8; IR (thin film, cm^{-1}) 3083, 2908, 2254, 1543, 1577; HRMS (TOF MS ES$^+$) m/z calculated for $C_{12}H_{11}N_3$ 220.0851, $[M+Na]^+$ found 220.0853; TLC R_f=0.2 (1:1 hexane/EtOAc).

4.2.13. 2-(1-Cyclohexylbut-3-enyl)malononitrile (**3i**)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 (dddd, J=17.1, 10.2, 8.6, 6.0 Hz, 1H), 5.28 (dd, J=17.0, 1.3 Hz, 1H), 5.23 (d, J=10.0 Hz, 1H), 3.91 (d, J=4.2 Hz, 1H), 2.57–2.50 (m, 1H), 2.31–2.23 (m, 1H), 1.96–1.86 (m, 2H), 1.85–1.65 (m, 4H), 1.36–1.04 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.3, 120.2, 112.9, 112.6, 45.4, 39.9, 33.7, 31.2, 29.7, 26.5, 26.3, 26.2, 24.7; IR (thin film, cm^{-1}) 2931, 2360, 1642, 1448; TLC R_f=0.8 (3:1 hexanes/EtOAc).

*4.2.14. 2-(1-(Naphthalen-2-yl)but-3-enyl)malononitrile (**3j**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92–7.82 (m, 4H), 7.57–7.49 (m, 3H), 5.70 (dddd, J=17.0, 10.1, 7.6, 6.6 Hz, 1H), 5.28 (dd, J=17.0, 1.3 Hz, 1H), 5.19 (d, J=10.1 Hz, 1H), 4.11 (d, J=5.8 Hz, 1H), 3.48 (add, J=13.6, 7.6 Hz, 1H), 2.92–2.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.9, 133.5, 133.4, 133.2, 129.4, 128.3, 128.0, 127.7, 126.9, 125.1, 120.1, 112.1, 111.8, 46.2, 36.7, 29.2; IR (thin film, cm^{-1}) 3060, 2923, 2254, 1510; HRMS (TOF MS ES$^+$) m/z calculated for $C_{17}H_{14}N_2$ 269.1055, $[M+Na]^+$ found 269.1058; TLC R_f=0.3 (4:1 hexanes/EtOAc).

*4.2.15. 2-Allyl-2-(1-(naphthalen-2-yl)but-3-enyl)malononitrile (**4j**)*

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97–7.89 (m, 3H), 7.84 (s, 1H), 7.62–7.53 (m, 3H), 5.95 (dddd, J=16.8, 9.7, 7.8, 7.3 Hz, 1H), 5.56 (dddd, J=16.9, 10.2, 6.9, 6.7 Hz, 1H), 5.45 (d, J=10.2 Hz, 1H), 5.35 (dd, J=17.0, 1.1 Hz, 1H), 5.15 (dd, J=17.0, 1.3 Hz, 1H), 5.00 (d, J=10.1 Hz, 1H), 3.32 (m, 3H), 3.06 (m, 2H), 2.60 (dd, J=13.9, 7.3 Hz, 1H), 2.45 (dd, J=13.9, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.6, 129.3, 129.1, 128.9, 128.3, 127.0, 127.0, 126.9, 125.9, 123.4, 118.8, 51.7, 43.4, 40.8, 36.5; IR (film, cm^{-1}) 3060, 2931, 2362, 1642; HRMS (TOF MS ES$^+$) m/z calculated for $C_{20}H_{18}N_2$ 309.1368, $[M+Na]^+$ found 309.1357; TLC R_f=0.4 (3:1 hexanes/EtOAc).

*4.2.16. Methyl 2-cyano-3-phenylhex-5-enoate (**3k**) (2:1 mixture of diastereomers)*

^{1}H NMR ($CDCl_3$, 500 MHz) major δ 7.38–7.26 (m, 5H), 5.73 (dddd, J=17.0, 10.2, 7.0, 6.9 Hz, 1H), 5.24 (dd, J=17.1, 1.4 Hz, 1H), 5.15 (d, J=10.3 Hz, 1H), 3.92 (d, J=5.3 Hz, 1H), 3.64 (s, 3H), 3.44 (ddd, J=7.8, 7.6, 5.0 Hz, 1H), 2.67 (t, J=7.8 Hz, 2H); minor δ 7.38–7.26 (m, 5H), 5.60 (dddd, J=17.1, 10.1, 7.1, 6.9 Hz, 1H), 5.14 (dd, J=15.7, 1.4 Hz, 1H), 5.02 (d, J=10.2 Hz, 1H), 3.73 (d, J=6.00 Hz, 1H), 3.71 (s, 3H), 3.48 (ddd, J=8.9, 7.6, 6.1, 6.1 Hz, 1H), 2.76–2.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 139.1, 138.4, 134.5, 134.3, 133.7, 131.3, 129.52, 128.3, 128.2, 128.1, 128.0, 119.2, 119.5, 115.7, 115.3, 53.6, 53.5, 45.6, 45.2, 44.4, 43.5, 37.7, 36.6; IR (thin film, cm^{-1}) 3066, 2956, 2846, 2250, 1747, 1436; HRMS (TOF MS ES$^+$) m/z calculated for $C_{14}H_{15}NO_2$ 252.1001, $[M+Na]^+$ found 252.0998; TLC R_f=0.4 (3:1 hexanes/EtOAc).

*4.2.17. 5-(1-Phenylbut-3-enyl)pyrimidine-2,4,6-triamine (**11**)*

A solution of guanidine hydrochloride (0.022 g, 0.022 mmol) in 0.350 mL of *t*-BuOH was added *t*-BuOK (0.022 mmol, 1.0 M solution in THF). In a separate flask, **3a** was diluted with 0.800 mL of *t*-BuOH and then added via syringe to the suspension of guanidine hydrochloride. This mixture was stirred at reflux for 2 h. The reaction was then cooled to room temperature, poured into 3 mL of H_2O and extracted with CH_2Cl_2 (3×5 mL), dried with Na_2SO_4, and concentrated in vacuo. Purification of the mixture by flash chromatography (10:1 CH_2Cl_2/MeOH) provided 0.021 g of **11** (86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, J=4.4 Hz, 4H), 7.27–7.24 (m, 1H), 5.86 (dddd, J=17.0, 10.1, 7.2, 6.7 Hz, 1H), 5.15 (dd, J=17.1, 1.3 Hz, 1H), 5.04 (dd, J=10.2, 0.7 Hz, 1H), 4.60 (br s, 2H), 4.42 (br s, 4H), 3.97 (dd, J=10.2, 5.8 Hz, 1H), 2.96–2.89 (m, 1H), 2.83–2.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5, 160.9, 142.1, 136.7, 129.2, 127.3, 127.1, 117.2, 91.1, 40.0, 34.4; IR (thin film, cm^{-1}) 3488, 3388, 3342, 3183, 2977, 2931, 1608, 1569, 1438; TLC R_f=0.3 (10:1 EtOAc/MeOH).

Acknowledgements

Support for this research has been provided by the University of California, Irvine. Amgen and Eli Lilly Foundation are gratefully acknowledged for additional research support. Dr. John Greaves is acknowledged for mass spectrometric data.

Supplementary data

Full spectroscopic data for new compounds can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.061.

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