ACS OMEGA

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Cite This: ACS Omega 2018, 3, 8937−8944

http://pubs.acs.org/journal/acsodf

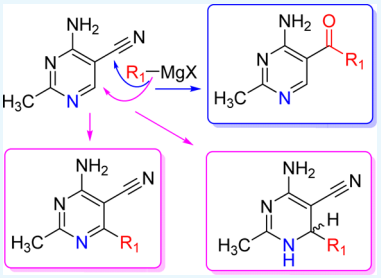
Unusual Nucleophilic Addition of Grignard Reagents in the Synthesis of 4-Amino-pyrimidines

Ryan A. J. Tinson, David L. Hughes, Leanne Ward, and G. Richard Stephenson*

School of Chemistry, University of East Anglia, Norwich Research Park, Norwich, Norfolk NR4 7TJ, U.K.

Supporting Information

ABSTRACT: Pyrimidines have always received considerable attention because of their importance in synthesis and elucidation of biochemical roles, in particular that of vitamin B1. Herein, we describe a reaction pathway in a Grignard reagent-based synthesis of substituted pyrimidines. A general synthesis of α-keto-2-methyl-4-amino pyrimidines and their C6-substituted analogues from 4-amino-5-cyano-2-methylpyrimidine is reported. The presence of the nitrile substituent in the starting material also results in an unusual reaction pathway leading to C6-substituted 1,2-dihydropyrimidines. Grignard reagents that give normal pyrimidine products under standard reaction conditions can be switched to give dihydropyrimidines by holding the reaction at 0 °C before quenching.



INTRODUCTION

The synthesis of pyrimidines has always been a priority topic for investigation because of their widespread use as scaffolds in medicinal, pharmaceutical, and academic chemistries. Recently, there has been a marked return to prominence of these structures, particularly in the functionalized amino pyrimidine series,[1] as synthetic targets. Although a majority of these examples are 2-amino pyrimidines, examples of 4-[2] and 6-aminopyrimidines[3] are also notable features. These vital building blocks of life are found in many biologically significant molecules, including structures like DNA **1**, drugs such as zidovudine **2**,[4,5] and barbiturate sodium thiopental **3** (Figure 1). Pyrimidines are also investigated for the treatment of the neurological disorders Beriberi and Korsakoff syndrome and as a recognition motif for binding in thiamine diphosphate-dependent enzymes (compound **4**, Figure 1).[6,7]

Because of their versatile hydrogen-bonding interactions, these small fragments have been intensively investigated by medicinal chemists during the past decade. Their applications in GSK's antimalaria drug trimethoprim **5**,[8] antibiotic bacimethrin **6**,[9] and in the treatments of thiamine deficiency,[10−12] are well-documented (Figure 2).

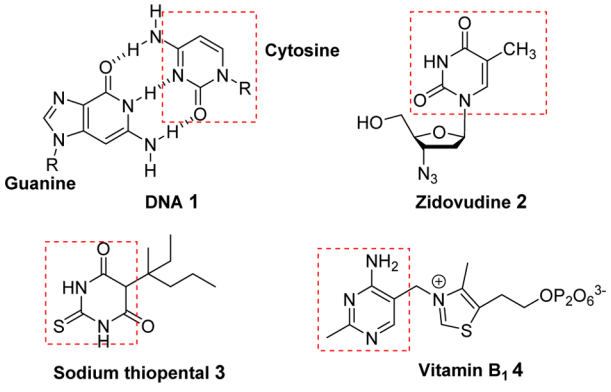


Figure 1. (a) DNA fragment, HIV drug zidovudine, sodium thiopental, and vitamin B_1.

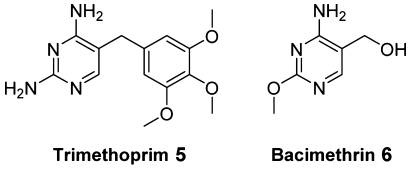


Figure 2. Aminopyrimidines in GSK's trimethoprim and antibiotic bacimethrin.

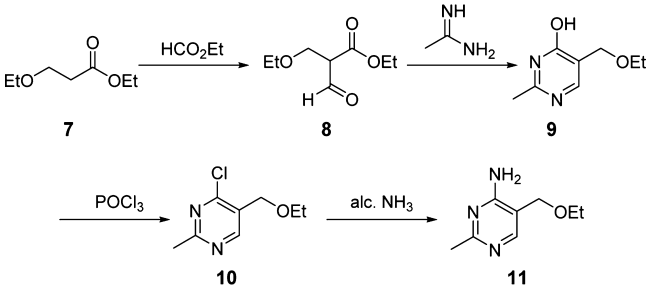
Commonly, the synthesis of pyrimidine rings utilizes a sodium alkoxide-catalyzed condensation reaction between urea, an aldehyde, and a malonic ester. Most methodologies to form these rings utilize this process, now called the Biginelli reaction.[13−15] Assembly of the core aromatic structure permits further functionalization with a range of reactive groups. The initial synthetic strategies to access the valuable 4-amino-2-methyl pyrimidine substitution pattern were originally developed by Williams[16] (Scheme 1). The reported procedure is outlined below and was subsequently modified by others for the development and production scale-up of vitamin B_1 synthesis.

Although the 4-amino-2-methyl pyrimidines have been investigated with many differing structural modifications,[17−19] there are very few examples for the synthesis of α-keto-4-amino-2-methyl pyrimidines and their analogues.[20] As the core pyrimidine ring is observed widely throughout nature, it was surprising to find such a lack of examples because these α-keto

Received: May 25, 2018
Accepted: July 18, 2018
Published: August 10, 2018

DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937−8944

Scheme 1. Williams' Synthesis of 4-Amino-2-methyl Pyrimidine

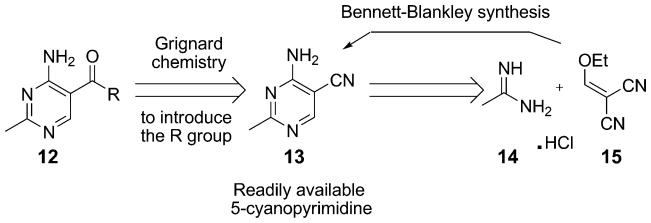


structural analogues could be good candidates for inhibitor mimics and for potential structural manipulations in structure–activity relationship studies. To address this issue, we have devised a new synthetic route, which uses cheap and readily available starting materials, to construct α-keto-4-amino-2-methyl pyrimidines.

RESULTS AND DISCUSSION

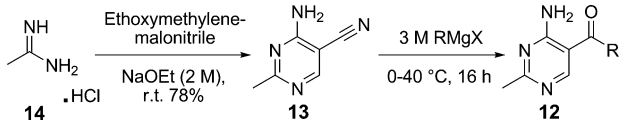
Our approach to α-keto-4-amino-2-methyl pyrimidines is based on the inclusion of a nitrile substituent at the 5-position to enable the introduction of a wide variety of R groups. This allows us to exploit the easy availability of 2-methyl-4-amino-5-cyano-pyrimidines (Scheme 2).[17]

Scheme 2. Synthetic Approach to Access α-Keto-4-amino-2-methyl Pyrimidines with a Wide Variety of R Groups



Thus, our synthesis of a range of differently substituted α-keto-2-methyl-4-amino pyrimidines began by employing the established condensation reaction of cheap and accessible reagents, acetamidine hydrochloride **14** and ethoxymethylene-malonitrile **15**, which after recrystallization of the crude product from ethanol gave the required nitrile **13** in a 78% yield (Scheme 3, step 1).[17]

Scheme 3. New Synthesis of the Pyrimidyl Ketones



We now turned to a series of preliminary experiments to assess the optimum temperature for addition of the Grignard reagent to the nitrile. Addition of the Grignard reagent at 0 °C and warming to 40 °C gave total consumption of the starting material after 16 h. Lower temperatures resulted in incomplete consumption and required longer reaction times. Addition of the appropriate Grignard reagent produced the desired keto products **12** with various R groups after simple column chromatography in yields of 16–68% (see Scheme 4 and Table 1, product type **A**). The infrared spectra of the products showed an unusually low position for the C=O stretching

Scheme 4. Surprising Range of Products Isolated from the Addition of Grignard Reagents to the Nitrile-Substituted Aminopyrimidine

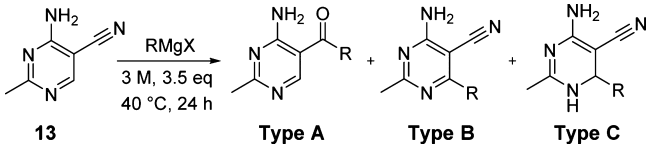
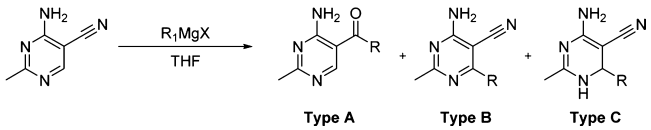


Table 1. Product Structures and Yields of Grignard Addition Products A, B, or C



entry	R	temp, °C	% yield (type A)	% yield (type B)	% yield (type C)
1	Me	0–40[a]	**18** (50%)[b]		
2	Me	40[c]			**17** (85%)
3	Et	0–40[a]	**19** (68%)[b]	**20** (27%)[d]	
4	Et	40[c]			**21** (80%)
5	Pr	0–40[a]	**22** (16%)[b]	**23** (20%)[d]	
6	Pr	0–25[e]			**24** (67%)
7	Pr	40[c]	**22** (22%)		
8	Bu	0–40[a]		**25** (18%)[d]	
9	Bu	0–25[e]			**26** (87%)
10	*i*-Pr	0–25[e]			**27** (56%)
11	*t*-Bu	40[c]			**28** (42%)
12	phenyl	0–40[a]	**29** (25%)[b]	**30** (40%)[d]	
13	phenyl	0–25[e]			**31** (81%)
14	vinyl	40[c]			**32** (76%)
15	HC≡C	40[c]			
16	HC≡C	0–25[e]			

[a]Grignard reagent was added at 0 °C, and the reaction mixture was then warmed to 40 °C and then left to cool and stirred at rt overnight. [b]By procedure I. [c]By procedure III (Grignard reagent was added at 40 °C). [d]By procedure II (like procedure I but neutralized with aqueous $NaHCO_3$, before extraction). [e]By procedure IV in which the reaction temperature was maintained at 0 °C for 3 h before being allowed to warm to rt overnight.

vibration of the ketones at about 1650 cm^{-1}. In the ^1H nuclear magnetic resonance (NMR) spectra, the signals for the NH_2 protons came at two separate chemical shifts, presumably because of H-bonding to the adjacent carbonyl oxygen by one of the protons of the amino substituent. This strong intramolecular hydrogen bonding also accounts for the unusual position of the C=O stretching vibration for these compounds and is consistent with the data reported for 1-(2-aminophenyl)ethanone.[21] During the purification of our ketone products, it became apparent that other byproducts had been formed during the Grignard reaction. Characterization of these byproducts allowed us to identify some unexpected structures, which reveal an unusual alternative pathway for the addition of the Grignard reagent at the C-6 position of the pyrimidine ring (Scheme 4, product types **B** and **C**).

The formation of these unexpected substitution patterns (see Scheme 4) was apparent from the lack of the C6 aromatic proton at ~8.0 ppm in the ^1H NMR spectrum and the retained

DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937–8944

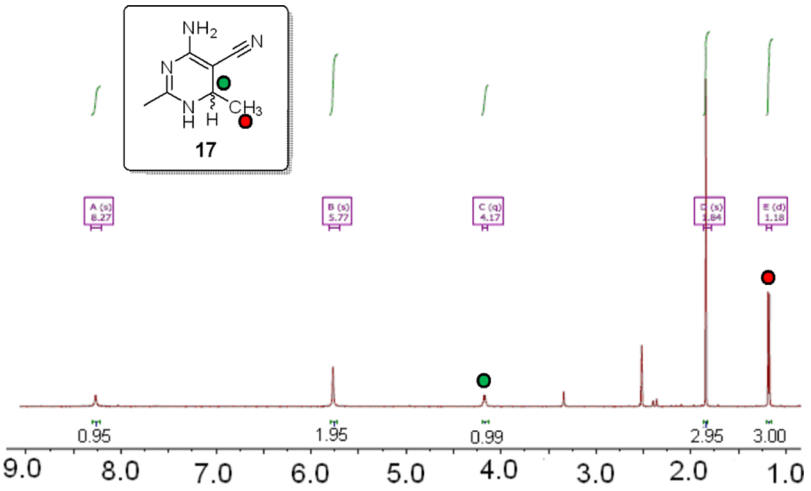


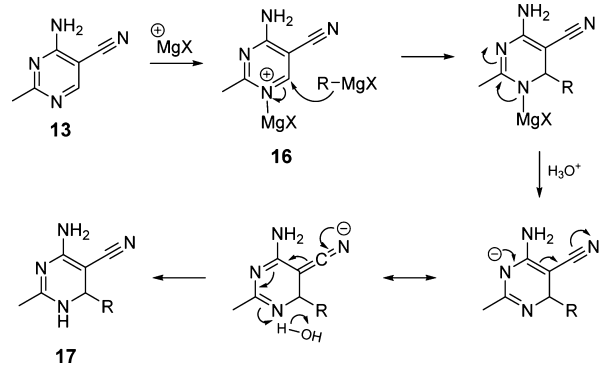
Figure 3. Structure of racemic **17** with the CHMe feature that gives a characteristic C6 quartet and C7 doublet in the ^{1}H NMR spectrum.

strong C≡N stretching vibration at 2100 cm^{-1} in the infrared spectrum. After adjusting the reaction conditions, addition of the methyl and ethyl Grignard reagents at 40 °C instead of 0 °C gave the [1,2]-dihydropyrimidine analogues of type **C** in good yields (80−85%). These structures were identified by the presence of the methyl signal as a doublet with ^3J coupling (6.0 Hz) to the CH proton (q, ^3J = 6.0 Hz) located at 4.1 ppm (e.g., see Figure 3). The assignment of these spectral features was confirmed by the analysis of ^{1}H correlation spectroscopy data. The [1,2]-dihydro products also retained the distinctive nitrile stretch at 2100 cm^{-1} in their infrared spectra. The key features discussed above allow the characterization data for the products of type **B**/**C** and the anticipated product of type **A** to be easily distinguished. Remarkably, these [1,2]-dihydro compounds remained stable at room temperature over a period of weeks, despite the loss of aromaticity following the addition of the Grignard reagent. Some aryl-[22] and ferrocenyl-substituted[23] examples appear to share the same stability shown by our nitrile-substituted structures, whereas Lyle[24] has reported instability in the cyano-substituted dihydropyridine analogues.

A plausible mechanism for the synthesis of side products of types **B**/**C** could arise as a consequence of the Schlenk equilibrium[25] between the Grignard reagent RMgX, R_2Mg, and MgX_2. Coordination of the Lewis acidic MgX_2 to the N1 nitrogen of the pyrimidine to form **16** would make the C6 position more electrophilic and hence promote attack by the Grignard reagent (Scheme 5). Moreover, an electron-withdrawing group adjacent to this position would further increase the electrophilicity of the C6 position providing an explanation for why, in the 5-cyano series, this side-reaction is far more favored. An alternative possibility, however, would be a radical mechanism for the transfer of the R group, followed by loss of H$^\bullet$ by an oxidative step to form **17**.

Examples of reactions that are capable of forming stereogenic centers from an aromatic system using Grignard reagents are rare, but a notable precedent for this type of transformation has been described in the synthesis of antifungal agent Voriconazole by Pfizer.[26] The methyl and ethyl C6-substituted analogues have been reported previously in the synthesis of vitamin B_1 analogues, but were acquired by condensation chemistry as described by Todd et al.[27,28] This condensation approach has not been applied to the synthesis of other analogues containing modifications at this position, so the new

Scheme 5. Proposed Mechanism of the formation of [1,2]-Dihydropyrimidine 17



examples described here, which are obtained by the Grignard approach, will open up a general access to this class of structures.

Interestingly, the Schlenk equilibrium is often controlled by changes to the Grignard reagent, solvent, or temperature. To assess the optimum conditions, a range of temperatures from (−78 to 40 °C) were tested, but this served only to increase the consumption of the starting nitrile **13** and did not affect the product outcome. It was noticeable that addition of the Grignard at 0 °C followed by warming to 40 °C gave a mixture of products, so some Grignard additions at 40 °C were attempted. As the Schlenk equilibrium should favor formation of the R_1MgX species at higher temperatures and in a polar aprotic solvent, the involvement of Lewis acidic MgX_2 could be reduced, and therefore C-6 addition should be decreased. This, however, with our initial choice of methyl and ethyl Grignard reagents, gave **17** and **21** as the sole products (Table 1, entries 2 and 4).

A range of solvents were then examined to assess their affect upon product distribution. As tetrahydrofuran (THF) had already been used for the preliminary experiments, we sought to decrease the solvent polarity. Diethyl ether was tested under the same conditions, and from the analysis of the ^{1}H NMR spectra, it was obvious that only methyl ketone and the unreacted starting material were present. Attempts using 1,4-dioxane resulted in the precipitation of the MgX_2 salts. Removal of these MgX_2 salts by filtration was expected to improve the selectivity for the formation of the ketone

DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937−8944

compound; however, this proved not to be the case, and the under these conditions, the attempted reaction gave only the recovered unreacted starting material.

On the basis of the mechanism proposed in Scheme 5, it seemed probable that the products that retained the nitrile group originated by initial addition of the nucleophile to the heteroaromatic ring (producing the [1,2]-dihydro product of type **C**) and that oxidation under the reaction conditions later resulted in rearomatization to give 5-cyano-6-alkyl-2-methyl-pyrimidine products of type **B**. This hypothesis was tested for Grignard reagents (R^1 = Et, Pr, Bu, and Ph; Table 1 entries 3, 5, 8, and 12) that tended to give low yields and only products of types **A** and **B**. By avoiding the high temperature of 40 °C and keeping the reaction mixture at 0 °C for 3 h, more time was allowed for the addition at C6 to go to completion before the reaction was quenched.

Under these conditions (Table 1, entries 6, 9, 10, and 13), the [1,2]-dihydro products of type **C** were isolated at moderate to good yields. Bulky Grignard reagents (branched R^1 groups such as *i*-Pr and *t*-Bu) give poorer results (56 and 42%, respectively). In the other cases, (R^1 = Me, Et, Pr, and Bu), the yields of the [1,2]-dihydro products ranged from 67 to 87%. Extending the study to phenyl- and vinylmagnesium bromide, we were able to show that the low temperature conditions worked well to improve the yields with phenylmagnesium bromide, giving [1,2]-dihydro product **31** in an 81% yield (compare entries 12 and 13), and our original 40 °C reaction conditions were suitable with vinylmagnesium bromide, giving **32** in a 76% yield.

On the basis of these trends, it appears that the unexpected formation of [1,2]-dihydropyrimidine is in fact the preferred addition pathway and proceeds efficiently, albeit slowly, at 0 °C. At higher temperatures, the addition at the nitrile begins to become significant, so that reactions that are allowed to warm up before all of the Grignard reagent has been consumed can produce substantial amounts of the ketones (type **A** products). Type **B** products in many cases arise by rearomatization of [1,2]-dihydropyrimidines, accounting for the failure to isolate type **C** products in these cases. In other cases, however, the addition of the Grignard reagent can be performed at 40 °C to give methyl- and ethyl-substituted [1,2]-dihydropyrimidines in a high yield. We proposed that this difference arises from the differences in stability of type **C** products under strong acid (HCl; entries 1, 3, 5, 8, and 12) conditions used in the quench, compared to the weak acid (ammonium chloride) used for entries 2, 4, 6, 7, 9, 10, 11, 13, and 14. Steric bulk in the nucleophile (e.g., entry 8) seems to block addition at the nitrile, and type **A** products were not formed with butylmagnesium bromide. Alkynyl Grignard reagents are less reactive and HC≡CMgBr failed to add to **13**, even at 40 °C.

Crystallization and X-ray analysis of the simple methyl substituted example **17** confirmed the [1,2]-dihydro structure and the presence of the stereogenic center at C6 (Figure 4). C6 is displaced 0.078(2) Å from the good mean plane of the rest of the heterocyclic ring, which supports the presence of extended π-overlap into the nitrile substituent. The shorter bond length of C1−C2 [1.379(2) Å] when compared to the C1−C6 bond of the C−CHMe [1.510(2) Å] suggests the presence of the alkene π bond in conjugation with the nitrile substituent within the aromatic π-system.

Measurement of the CN bond length C11−N12 [1.158(2) Å] indicates a typical length for this group, although the C1−C11 C−CN [1.402(2) Å] bond length lies between a normal

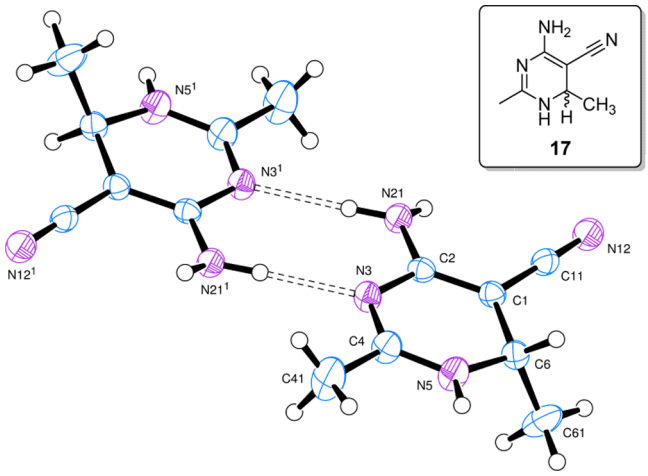


Figure 4. diagram for the crystal structure of 4-amino-2-methyl-5-cyano-6-methyl-[1,2]-dihydropyrimid-ine **17**. Thermal ellipsoids are drawn at the 50% probability level.

C−C bond (1.5 Å) and an sp^2 C=C (1.3 Å), thereby suggesting the presence of a partial sp^2 bond character between the aromatic π-system and the nitrile bond. At C6, the CHMe position adopts the classic tetrahedral geometry with a bond angle for the atom group N5−C6−H6 at 109.0(9)° and the bond length for C1−C6 at 1.510(2) Å, whereas the shorter bonds between the sp^2 centers of C1−C2 and C4−N3 have lengths of 1.379(2) and 1.312(2) Å, respectively. Interestingly, these structures form a hydrogen-bonded dimer pair (racemic, with *R* and *S* configurations) around a center of symmetry, forming a binding pattern similar to that observed in DNA base pairs (Figure 4), which becomes extended through further pairs of hydrogen bonds (see the Supporting Information).

This paper identifies three competing pathways for the addition of Grignard reagents to the readily available 4-amino-2-methyl-5-cyanopyrimidine starting material, giving access to either the sought after α-keto-4-amino-2-methyl pyrimidines or alternative products arising from substitution of the pyrimidine ring itself. Especially in the cases where the exclusive formation of a single product has been identified, the results presented here should open the way for the exploitation of these substitution patterns in future research. Furthermore, studies are now in progress to extend the range of examples that give exclusively the unusual chiral 1,2-dihydropyrimidines to introduce alternative reactive functional groups at the C6 position (e.g., alkynes) to prepare the way for the development of an enantioselective version of the procedure.

Ideally, this research would facilitate a wider range of ongoing synthetic modifications such as Diels−Alder cycloaddition chemistry and metal-catalyzed cross-coupling reactions, which could utilize the vinyl adduct **32**. Each in their own way, the intended α-keto products and the unusual ring-substituted products are ideal structures to access a wide range of pyrimidine-derived compounds that will be of value in medicinal and bioorganic chemistry. Our procedure avoids the need for extensive purification steps and so provides a potential "gateway compound" suited for easy functionalization in future studies. It also offers potential access to key intermediates in the substantial quantities needed for sustained biochemical/pharmaceutical research projects and scale-up processes.[29] Furthermore, the ketones made available in this way would be suitable prochiral candidates for reductions to provide useful

DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937−8944

intermediates for the chiral synthetic pool and/or enzymatic studies.[30,31]

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out in dry solvents, unless otherwise stated. Anhydrous THF, diethyl ether, and toluene were distilled over sodium following literature methods. All solvents and chemicals were purchased from appropriate suppliers including Sigma-Aldrich, Acros, TCI, Fluorochem, Alfa Aesar, and Fisher. Infrared spectra were obtained on a PerkinElmer spectrum 100 Fourier transform infrared spectrometer, with most compounds dissolved in dichloromethane and measured as a film on a NaCl disc. In cases where compounds were not soluble in this solvent, the infrared spectrum was obtained using an attenuation total reflection plate. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker (Ascend) 500 MHz spectrometer and a sample express autosampler. Mass spectra were measured by the EPSRC UK National Mass Spectrometry Facility, Swansea, UK using an LTQ Orbitrap XL spectrometer. Melting points were recorded on a BUCHI melting point apparatus B545. X-ray diffraction data were recorded at the UEA on an Oxford Diffraction Xcalibur-3/Sapphire3 CCD diffractometer. The data were then processed with the CrysAlisPro-CCD and -RED programs.[32,33] The structure was determined by the direct method routines in the SHELXS program[34] and refined by full-matrix least-squares methods on F^2's in SHELXL[34] using WinGX.[35] Scattering factors for neutral atoms were taken from the International Tables for X-ray Crystallography.[36]

*Preparation of 4-Amino-5-cyano-2-methylpyrimidine (**13**).*[17] Sodium (0.19 g) was added in small pieces to ethanol (4.0 mL) to produce a 2 M solution of sodium ethoxide. Then, acetamide hydrochloride (0.80 g, 8.50 mmol) was added. Filtration through celite gave a clear solution, which upon addition of ethoxymethylene malonitrile (0.50 g, 4.10 mmol) produced a yellow precipitate that was collected by filtration and recrystallized from ethanol to give the title compound as fine yellow needles (1.10 g, 70%). mp 245−247 °C [lit.[17] mp 246−248 °C]. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.52 (s, 1H), 7.77 (s, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.6, 162.8, 161.6, 116.2, 87.1, 26.4 ppm. IR ν_{max}: 3378, 3334 (NH_2), 2223 (sp CN), 1672, 1584, 1542 (C−H, sp^2 stretch) cm^{-1}.

Preparation of tert-Butylmagnesium Bromide. 2-Methyl-2-bromopropane (1.0 mL, 8.9 mmol, 1 equiv) in dry THF (9.0 mL) was added dropwise to a predried round-bottom flask containing magnesium turnings (427 mg, 17.8 mmol, 2.0 equiv) in anhydrous THF (20 mL). After activation with a small amount of iodine, addition was maintained to keep a gentle reflux. The reaction was then stirred at room temperature (rt) for 3 h. The Grignard reagent was titrated against 1,10-phenanthroline and isopropyl alcohol.

Typical Procedure I for the Synthesis of α-Keto-4-amino-2-methylpyrimidines (Products of Type A). *5-(4-Amino-2-methylpyrimidinyl)propan-1-one (**19**).* To 4-amino-5-cyano-2-methylpyrimidine **13** (200 mg, 1.5 mmol) in THF (5 mL) was added ethylmagnesium bromide in THF (3 M, 5.3 mmol, 1.74 mL, 3.5 equiv) dropwise at 0 °C. The reaction mixture was warmed to 40 °C and left to stir overnight. The reaction was then quenched with 1 M HCl (10 mL), stirred for a further 24 h, and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated under pressure to leave a fine powder. Column chromatography on silica eluting with EtOAc/hexanes (1:3 v/v) gave the product as a white solid (168 mg 68%). Rf = 0.6 EtOAc/hexanes 1:3 v/v. mp 160−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.62 (s, 1H), 5.67 (s, 2H), 2.87 (q, ^{3}J = 7.3 Hz, 2H, H-4), 2.47 (s, 3H, H-1), 1.15 (t, ^{3}J = 7.3 Hz, 3H, H-5) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.4, 171.1, 161.9, 158.9, 109.2, 29.5, 26.4, 8.1 ppm. IR ν_{max}: 3385, 3263, 3109, 2980 (sp^3 C−H stretch), 1657, 1625, 1528 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_8H_{12}N_3O$, 166.0975; found, 166.0972.

Typical Procedure II for the Synthesis of 4-Amino-5-cyano-2-alkyl- or 2-Arylpyrimidines (Products of Type B). *4-Amino-5-cyano-2-methyl-6-phenylpyrimidine (**30**).*[32] To 4-amino-5-cyano-2-methylpyrimidine **13** (200 mg, 1.5 mmol) in THF (5 mL) was added phenylmagnesium bromide in THF (3 M, 5.2 mmol, 1.74 mL, 3.5 equiv) dropwise at 0 °C. The reaction was warmed to 40 °C and left to stir overnight, then quenched with 1 M HCl (10 mL), and stirred for a further 24 h. The reaction was then neutralized with aqueous $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to leave a fine powder. Column chromatography on silica eluting with EtOAc/hexanes (gradient, 5:1 v/v to pure EtOAc) gave the product as a white powder (315 mg, 40%). Rf = 0.2 EtOAc/hexanes 5:1. v/v. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.87−7.82 (m, 2H), 7.63−7.51 (m, 3H), 2.47 (s, 3H) ppm (this compound would only dissolve in DMSO-d_6; signals for the NH_2 protons were not observed because of exchange with H_2O in the solvent). ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.7, 168.4, 164.7, 136.8, 131.3, 129.4, 129.0, 116.7, 84.2, 26.4 ppm. IR ν_{max}: 3379, 3330 (NH_2), 2168 (sp CN), 1680, 1626, 1561 cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}N_4$, 211.0978; found, 211.0978.

Typical Procedure III for the Synthesis of 4-Amino-5-cyano-2-methyl-6-alkyl- or 6-Alkenyl-[1,2]-dihydropyrimidines at 40 °C (Products of Type C). *4-Amino-5-cyano-2-methyl-6-vinyl-[1,2]-dihydropyrimidine (**32**).* To 4-amino-5-cyano-2-methylpyrimidine **13** (2.5 g, 19 mmol, 1 equiv) in THF (50 mL) was added vinylmagnesium bromide in THF (3 M, 65 mmol, 21.8 mL, 3.5 equiv) dropwise at 40 °C. The reaction mixture was left to stir overnight and then quenched with saturated aqueous ammonium chloride (20 mL) at 0 °C and stirred for further 48 h and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the product as a fine yellow powder (2.24 g, 76%). mp 171−173 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.47 (br s, 1H), 5.88 (s, 2H), 5.76 (ddd, ^{3}J = 16.9, 9.9, 6.9 Hz, 1H), 5.07−5.00 (m, 2H), 4.49 (d, ^{3}J = 6.9 Hz, 1H), 1.88 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.8, 159.4, 139.9, 122.1, 114.3, 52.5, 51.4, 21.8 ppm. IR ν_{max}: 3316, 3302 (NH_2), 2171 (sp CN), 1734 (sp^2 CO), 1683, 1638, 1601 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_8H_{11}N_4$, 163.0978; found, 163.0975.

Typical Procedure IV for the Synthesis of 4-Amino-5-cyano-2-methyl-6-alkyl- or 6-Alkenyl-[1,2]-dihydropyrim-idines from 0 °C to rt (Products of Type C). *4-Amino-5-cyano-2-methyl-6-propyl-[1,2]-dihydropyrimidine (**24**).* To 4-amino-5-cyano-2-methylpyrimidine **13** (200 mg, 1.5 mmol) in anhydrous THF (5 mL) at 0 °C was added propylmagne-

DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937−8944

sium chloride (2 M, 5.2 mmol, 2.6 mL, 3.5 equiv) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then left to warm to rt overnight. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous ammonium chloride (10 mL) and left to stand for 3 h. The product was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated to dryness to give the title compound as a fine yellow powder (180 mg, 67%). mp 163−165 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (s, 1H), 5.74 (s, 2H), 4.04 (dd, J = 18.8, 4.6 Hz, 1H), 1.84 (s, 3H), 1.46−1.23 (m, 4H), 0.92−0.88 (m, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.4, 160.1, 122.6, 51.7, 49.3, 41.4, 22.2, 16.9, 14.2 ppm. IR ν_{max}: 3310, 3252 (NH_2), 2100 (CN), 1650, 1617, 1538 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_9H_{15}N_4$, 179.1291; found, 179.1291.

Synthesis of α-Keto-4-amino-2-methylpyrimidines. *5-(4-Amino-2-methylpyrimidinyl)ethanone (**18**).* Following procedure I, using methylmagnesium bromide followed by column chromatography on silica eluting with ethyl acetate/hexanes (1:3 v/v) gave the title compound as a white solid (470 mg, 50%). mp 170−172 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.57 (s, 1H), 5.72 (s, 1H), 2.50 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.2, 171.4, 161.8, 159.8, 109.8, 26.6, 26.1 ppm. IR ν_{max}: 3372, 3114, 1651 (sp^2 C═O), 1590, 1520 (sp^2 C−H aromatic stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_7H_{10}N_3O$, 152.0818; found, 152.0815.

*5-(4-Amino-2-methylpyrimidinyl)butan-1-one (**22**).* Following procedure I, using *n*-propylmagnesium bromide followed by column chromatography on silica eluting with EtOAc/hexanes (2:1 v/v) gave the title compound as a white solid (43 mg, 16%). Rf = 0.3 EtOAc/hexanes 2:1 v/v. mp 147−149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 2.81 (t, ^3J = 7.4 Hz, 3H), 2.50 (s, 3H), 1.73−1.64 (m, 2H, H-5), 0.94 (t, ^3J = 7.4 Hz, 3H, H-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.6, 170.5, 162.0, 158.2, 109.3, 40.3, 25.8, 17.9, 13.8 ppm. IR ν_{max}: 3373, 3265 (NH_2) 1653, 1629, 1534 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_9H_{14}N_3O$, 180.1131; found, 180.1129.

This product was also obtained following procedure III; using *n*-propylmagnesium bromide followed by column chromatography on silica eluting with EtOAc/hexanes (2:1 v/v) gave the title compound as a white solid (60 mg, 22%).

*5-(4-Amino-2-methylpyrimidinyl)phenone (**29**).* Following procedure I, using phenylmagnesium bromide followed by column chromatography on silica eluting with EtOAc/hexanes (gradient, 5:1 v/v to pure EtOAc) gave the title compound as a white powder (200 mg, 25%), Rf = 0.5 EtOAc/hexanes 5:1 v/v. mp 182−184 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.33 (s, 1H), 8.12 (s, 2H), 7.68−7.63 (m, 3H), 7.61−7.54 (m, 2H), 2.45 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 196.2, 170.63, 162.8, 161.8, 138.6, 132.5, 129.4, 129.0, 108.9, 26.3 ppm. IR ν_{max}: 3381, 2925, 1627, 1577, 1598 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}N_3O$, 214.0975; found, 214.0973.

Synthesis of 4-Amino-5-cyano-2-alkyl- or 2-Arylpyrimidines. *4-Amino-5-cyano-6-ethyl-2-methylpyrimidine (**20**).*[27] Following procedure II, using methylmagnesium bromide followed by column chromatography on silica eluting with EtOAc/hexanes (gradient, 1:1 v/v to pure EtOAc) gave the title compound as a white powder (66 mg, 27%). Rf = 0.7 EtOAc/hexanes 1:1 v/v. mp 197−199 °C [lit.[27] mp 193−194 °C]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.42 (s, 2H), 2.66 (q, ^3J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.16 (t, ^3J = 7.6 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 170.4, 163.3, 115.3, 86.3, 30.6, 26.4, 12.8 ppm. IR ν_{max}: 3377, 3340 (NH_2), 2223 (CN), 1682, 1553, 1577 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_8H_{11}N_4$, 163.0978; found, 163.0974.

*4-Amino-5-cyano-2-methyl-6-propylpyrimidine (**23**).* Following procedure II, using *n*-propylmagnesium bromide followed by column chromatography on silica eluting with EtOAc/hexanes (2:1 v/v) gave the title compound as a yellow/white powder (53 mg, 20%). Rf = 0.6 EtOAc/hexanes 2:1 v/v. mp 176−177 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (s, 2H), 2.71 (t, ^3J = 10 Hz, 2H), 2.47 (s, 3H), 1.75−1.66 (m, 2H), 0.94 (t, ^3J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.0, 169.1, 162.1, 114.1, 85.6, 37.5, 25.1, 21.2, 12.4 ppm. IR ν_{max}: 3368, 3338 (NH_2) 1653, 1629, 224 (CN), 1678, 1553, 1417 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_9H_{13}N_4$, 177.1135; found, 177.1133.

*4-Amino-6-butyl-5-cyano-2-methylpyrimidine (**25**).* Following procedure II, using *n*-butylmagnesium bromide followed by column chromatography on silica eluting with EtOAc/hexanes (gradient, 1:1 v/v to pure EtOAc) gave the title compound as a white solid (50 mg, 18%). Rf = 0.6 EtOAc/hexanes 1:1 v/v. mp 180−182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69 (s, 2H), 2.72 (t, ^3J = 10 Hz, 2H), 2.46 (s, 3H), 1.68−1.60 (m, 2H), 1.40−1.31 (m, 2H), 0.88 (t, ^3J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.2, 170.4, 163.6, 116.0, 87.1, 37.0, 31.6, 26.8, 23.1, 14.2 ppm. IR ν_{max}: 3339, 3379, 2227 (sp CN), 1687, 1559, 1461 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_{10}H_{15}N_4$, 191.1291; found, 191.1289.

Synthesis of 4-Amino-5-cyano-2-methyl-6-alkyl- or -6-Phenyl- or 6-Alkenyl-[1,2]-dihydropyrimdines. *4-Amino-5-cyano-2,6-dimethyl-[1,2]-dihydropyrimidine (**17**).* Following procedure III, using methylmagnesium bromide gave the title compound as a fine yellow powder (2.4 g, 85%). mp 221−222 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.27 (s, 1H), 5.77 (s, 2H), 4.17 (q, ^3J = 6.0 Hz, 1H), 1.84 (s, 3H), 1.18 (d, ^3J = 6.0 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.0, 159.7, 122.4, 53.6, 45.5, 25.5, 22.1 ppm. IR ν_{max}: 3399, 3304, 2152 (sp CN), 1658, 1608, 1563 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_7H_{11}N_4$, 151.0978; found, 151.0975.

*4-Amino-5-cyano-6-ethyl-2-methyl-[1,2]-dihydropyrimidine (**21**).* Following procedure III, using ethylmagnesium bromide gave the title compound as a fine yellow powder (2.1 g, 80%). mp 213−215 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.19 (s, 1H, H-6), 5.75 (s, 2H, H-2), 4.09 (td, ^3J = 4.6, 2.3 Hz, 1H), 1.86 (s, 3H), 1.50−1.38 (m, 2H), 0.86 (t, ^3J = 7.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.5, 160.3, 122.7, 51.0, 50.6, 31.2, 21.7, 8.1 ppm. IR ν_{max}: 3372, 3326 (NH_2), 2180, 2149 (sp CN), 1659, 1600, 1565 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_8H_{13}N_4$, 165.1135; found, 165.1135.

*4-Amino-6-butyl-5-cyano-2-methyl-[1,2]-dihydropyrimidine (**26**).* Following procedure IV, using *n*-butylmagnesium bromide gave the title compound as a fine yellow powder (250 mg, 87%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (s, 1H), 5.74 (s, 2H), 4.08 (td, J = 4.8, 2.4 Hz, 1H), 1.86 (s, 3H), 1.45−1.40 (m, 2H), 1.34−1.25 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO): δ 161.1, 160.2,

DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937−8944

122.3, 51.3, 49.6, 38.4, 25.4, 22.8, 21.9, 14.5 ppm. IR ν_{max}: 2159 (sp CN), 1631, 1588, 1520 cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_{10}H_{17}N_4$, 193.1448; found, 193.1447.

*4-Amino-5-cyano-2-methyl-6-iso-propyl-[1,2]-dihydropyrimidine (**27**).* Following procedure IV, using *iso*-propylmagnesium bromide gave the title compound as a fine yellow powder (150 mg, 56%) mp 170−171 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 5.75 (s, 2H), 3.89 (d, J = 2.6 Hz, 1H), 1.87 (s, 3H), 1.57 (s, 1H), 0.86 (d, 3H), 0.82 (d, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.1, 160.8, 123.0, 55.4, 49.9, 36.7, 21.7, 17.3, 16.4 ppm. IR ν_{max}: 3368, 3321 (NH_2), 2175 (CN), 1652, 1601, 1565 (sp^2 C−H stretch) cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_9H_{15}N_4$, 179.1291; found, 179.1290.

*4-Amino-5-cyano-2-methyl-6-tert-butyl-[1,2]-dihydropyrimidine (**28**).* Following procedure III, using *tert*-butylmagnesium bromide gave the title compound as a fine yellow powder (120 mg, 42%). mp 217−219 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 8.38 (s, 1H), 5.82 (s, 2H), 3.61 (s, 1H), 1.96 (s, 3H), 0.85 (s, 9H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.9, 161.6, 124.2, 58.9, 48.9, 40.8, 25.0, 21.9 ppm. IR ν_{max}: 2159 (sp CN), 1637, 1598, 1562 cm^{-1}. HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_{10}H_{17}N_4$, 193.1448; found, 193.1445.

*4-Amino-5-cyano-2-methyl-6-phenyl-[1,2]-dihydropyrimidine (**31**).* Following procedure IV, using phenylmagnesium bromide gave the title compound as a fine yellow powder (256 mg, 81%). ^1H NMR (400 MHz, DMSO-d_6): δ 8.79 (br s, 1H), 7.4−7.37 (m, 2H), 7.31−7.27 (m, 3H), 5.91 (s, 2H), 5.11 (s, 1H), 1.92 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 145.9, 129.4, 129.0, 128.2, 127.9, 127.2, 127.0, 122.4, 53.8, 22.1. IR ν_{max}: 3345, 3317 (NH_2), 2123 (CN), 1646, 1601, 1550 (sp^2 C−H stretch) cm^{-1} HRMS (ESI-LTQ Orbitrap XL) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}N_4$, 213.1135; found, 213.1137.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01137.

Copies of ^1H and ^{13}C NMR spectra for all new compounds and X-ray structure details for compound **17** (PDF)

Crystallographic data for compound **17** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: g.r.stephenson@uea.ac.uk.

ORCID

G. Richard Stephenson: 0000-0003-1487-9178

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript, and all authors have contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EU Interreg Trans Manche/Channel cross-border project "Academy-Industry Chemistry Channel" (AIcc: ref 4196) for the financial support and the EPSRC mass spectrometry facility at the University of Swansea for HRMS data.

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DOI: 10.1021/acsomega.8b01137
ACS Omega 2018, 3, 8937−8944