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Annulation of Thioimidates and Vinyl Carbodiimides to Prepare 2-Aminopyrimidines, Competent Nucleophiles for Intramolecular Alkyne Hydroamination. Synthesis of (−)-Crambidine

Nicholas R. Perl, **Nathan D. Ide**, **Sudeep Prajapati**, **Hahdi H. Perfect**, **Sergio G. Durón**, and **David Y. Gin***
Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, and the Department of Chemistry, University of Illinois, Urbana, IL 61801

Certain members of the crambescidin natural products,[1–5] derived from the marine sponge *Crambe crambe*, have exhibited remarkable biological properties, including anticancer, anti-HIV, antifungal, and Ca^{2+} ion channel blocking activities. Many compounds within this class are characterized by a polycyclic guanidine core linked to a hydroxyspermidine moiety by a linear ω-hydroxy fatty acid. Crambidine (**1**› Figure 1) is atypical within this family of alkaloids in that it possesses a fused *pyrimidine* heterocyclic core, while most of its other congeners exist in more highly reduced forms. Several elegant strategies have been reported for the synthesis of crambescidin alkaloids.[6–9] However, only a single reported synthesis of crambidine (**1**) has appeared,[10] involving dihydropyrimidine construction via Biginelli condensation, followed by oxidation. We report herein a synthesis of (−)-crambidine that capitalizes on two key processes, including a [4+2] annulation of thioimidates with vinyl carbodiimides and a hydroamination of alkynes with 2-aminopyrimidine nucleophiles.

Vinylcarbodiimides derived from pyrimidine-diones have been shown to converge with *O*-methyl imidates to furnish 2-aminopyrimidines.[11] However, when this annulation process was applied to vinylcarbodiimides and *O*-imidates more appropriate to the synthesis of **1**, the reaction was inefficient. For example, heating a mixture of *O*-methyl imidate **2** (Scheme 1A) with benzylvinylcarbodiimide **4** at elevated temperature in C_6D_6 for 24 h provided only 24% conversion to the 2-aminopyrimidine **5**. By contrast, when the corresponding thiomethyl imidate **3** was exposed to carbodiimide **4** under otherwise identical conditions, conversion to the pyrimidine **5** was accomplished with marked improvement (59%). Addition of the thiol scavenger AgOTf further enhanced the efficiency of the thioimidate annulation, allowing for the preparation of a variety of bicyclic 2-aminopyrimidines (Scheme 1B, **8**–**10**).

Extension of this [4+2] annulation reaction to access a complex substrate more suited to the synthesis of **1** commenced with the synthesis of a fully elaborated vinyl carbodiimide **14** (Scheme 2). Silyl ether **11**, obtained in enantiopure form according to the procedure of Campagne and coworkers,[12] was acylated with allyl chloroformate to afford the propargylic ester **12**. This intermediate was subjected to conjugate addition with azide to afford a separable *E*/*Z* mixture (2:1) of the corresponding β-azidoacrylate **13**. Reduction of the azide in *(E)*-**13** with PPh_3, followed by condensation with $TBSOCH_2N{=}C{=}O$, provided the vinyl carbodiimide **14**. Importantly, advancement of *(Z)*-**13** under analogous conditions also led to the formation of the *(E)*-isomer of **14** in similar yield, wherein stereochemical convergence occurs at the iminophosphorane stage.

gind@mskcc.org.

Supporting Information Available: Experimental details (PDF). This information is available at http://pubs.acs.org.

Synthesis of an initial crambidine-relevant thioimidate employed methyl thioimidate **15**[13] (Scheme 3). This served as a suitable acylation agent for the alkyl lithium species derived from the homoallylic iodide **16**, prepared in a manner similar to that described by Overman.[14] The resulting keto-thioimidate **17** was then heated with vinyl carbodiimide **14** to effect [4+2] annulation. Unfortunately, the bicyclic pyrimidine **18** was not observed; instead, the sole isolable product was pyrimidine **19**, presumably a result of C9–C10 β-elimination of the heterocycle in **18**.[7]

Given that the fragmentation (**18**→**19**) and concomitant destruction of the C10 stereoconfiguration could not be avoided, attention turned to thioimidate **26** (Scheme 4) as an alternate annulation substrate in which the internal alkyne would serve as a less acidic ketone surrogate. Thus, *Z*-selective Wittig olefination of (*S*)-2-(*t*-butylsilyloxy)butyraldehyde (**20**) with the phosphonium ylide derived from 4-(triphenylphosphonium)but-1-yne bromide (**21**) afforded enyne **22**. Following iodination of the terminal alkyne, the alkynyl iodide **23** was subjected to a sequence involving: (1) Cu-mediated coupling with pyrrolidinone **24** to afford internal alkyne **25**; (2) a two step conversion of the lactam **25** to the thioimidate **26** via carbonyl thionation and *S*-alkylation; (3) [4+2] annulation with vinylcarbodiimide **14** to furnish bicyclic pyrimidine **27**; and (4) chemoselective *N*-deprotection to provide the free 2-aminopyrimidine **28**, a substrate poised for intramolecular alkyne hydroamination.

Transition metal catalyzed hydroamination of alkynes[15, 16] is a powerful reaction in synthesis;[17–19] however, the paucity of guanidine or 2-aminopyrimidine nucleophiles engaging in this reaction is notable. After extensive experimentation, this transformation was validated by treatment of alkyne **28** (Scheme 4) with 10 mol% $AuCl_3$[20] at 40 °C, leading to efficient production of the tricyclic pyrimidine **29** as a single isomer (78%).

Subsequent spiroaminal formation at C8 in enamine **29** was conducted under carefully controlled acidic conditions, being mindful of the possibility of undesired C10-*N* bond rupture via potential C8-iminium reactivity. This liability was precluded by treatment with TsOH, effecting TBS removal and spirocyclization to provide the tetracyclic pyrimidinium **30** (77%).[21] The final stages of the synthesis involved conversion of the allyl ester **30** to its Cs-carboxylate. This nucleophile, obtained from carboxylic acid **31**, was amenable to selective alkylation with iodide **32**.[13] The resulting ester **33** was then subjected to *t*-butylcarbamate removal to afford (−)-crambidine (**1**).

A convergent synthesis of crambidine has been described, showcasing a [4+2] thioimidate-vinyl carbodiimide annulation and an intramolecular alkyne-guanidine hydroamination. This strategy should not only prove useful for preparing other members of the crambescidins, but also provide an attractive means with which to access complex *N*-heterocycles in general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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21. This and subsequent aminopyrimidine intermediates were purified by RP-HPLC (water/MeCN/TFA).

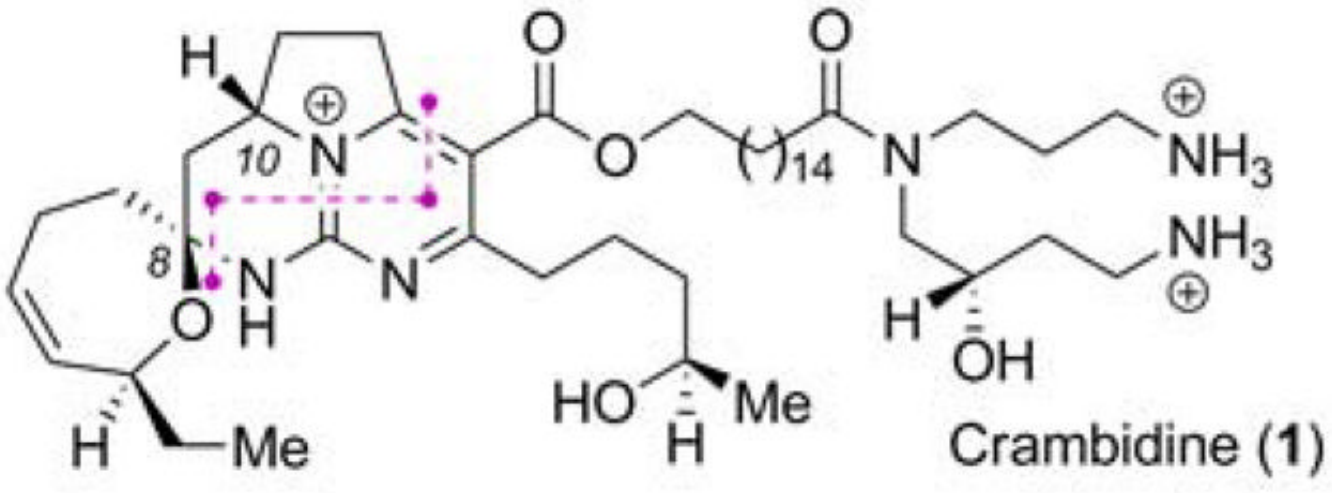
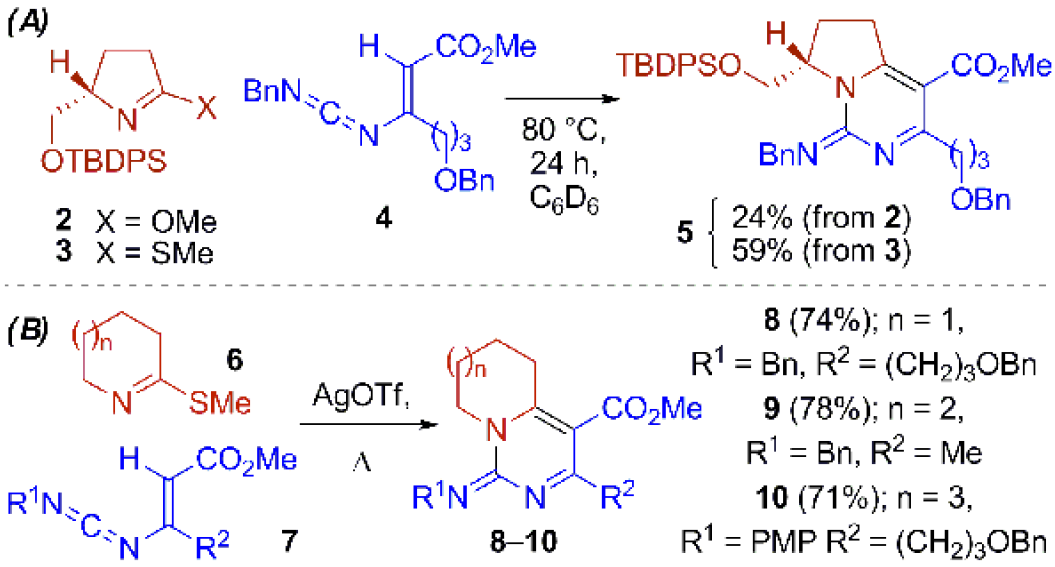
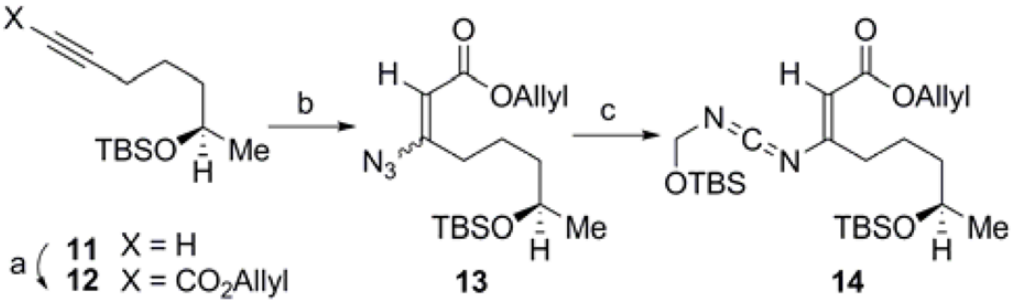


Figure 1.

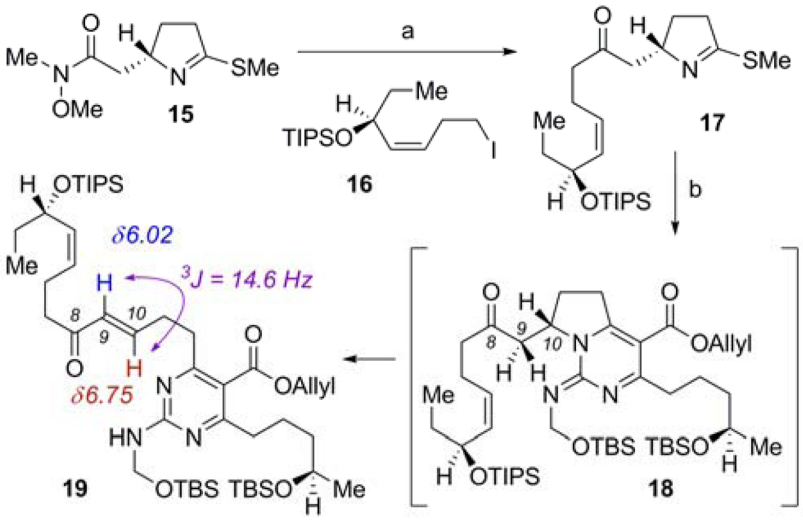


Scheme 1.



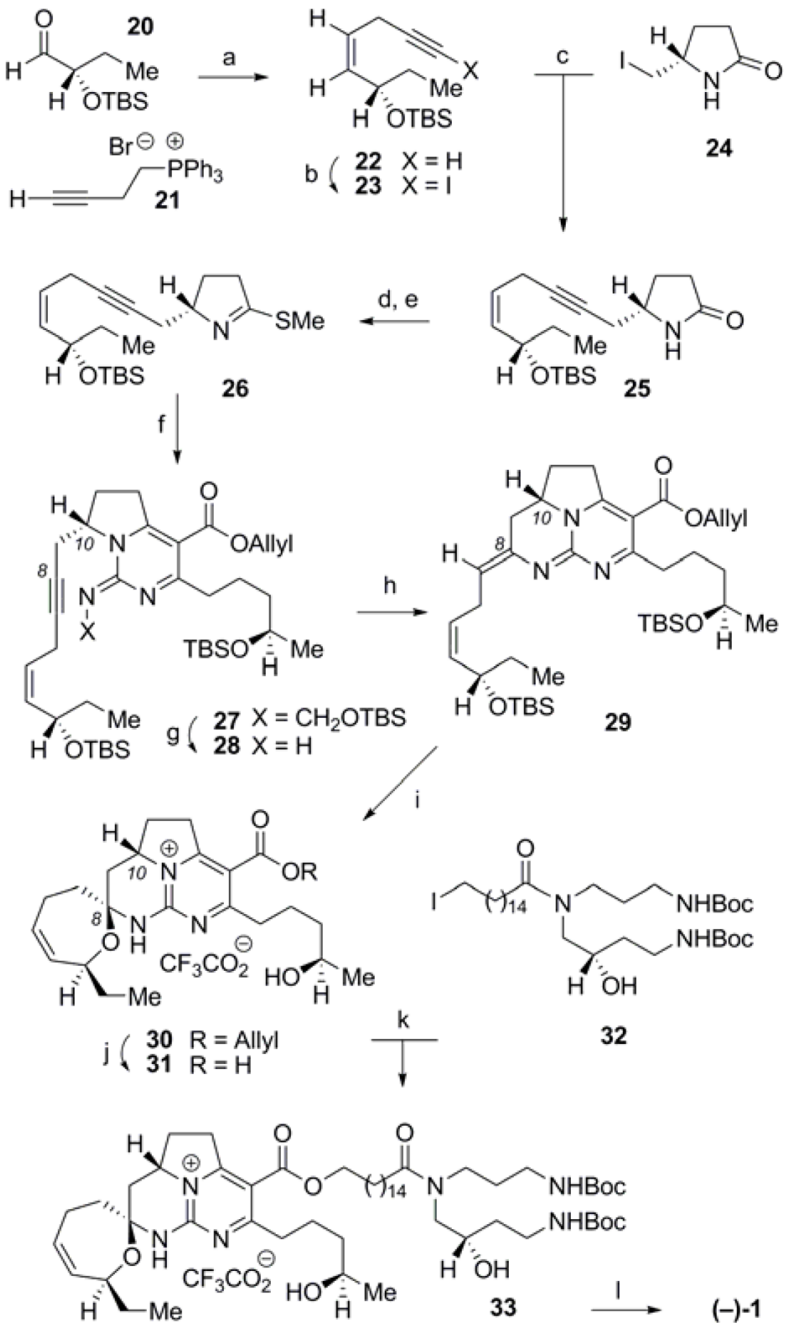
Scheme 2a.

[a]Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; AllylOCOCl, 90%; (b) $(Me_2N)_2C{=}NH_2N_3$, $CHCl_3$, 23 °C, 69% (2:1, *E*:*Z*); (c) PPh_3, CH_2Cl_2, 23 °C; add $TBSOCH_2N{=}C{=}O$, PhH, 80 °C, 49% from *(E)*-**13**, 43% from *(Z)*-**13**.



Scheme 3a.

[a]Reagents and conditions: (a) **16**, *t*-BuLi, Et_2O, Hexanes, −78 °C; add **15**, −78 → 23 °C, 67%; (b) **14** (2 equiv), $(CH_2Cl)_2$, 60 °C, 70%.



Scheme 4a.

[a]Reagents and conditions: (a) **21**, *n*-BuLi, THF, −78 → 0 °C; add **20**, −78 → 23 °C, 85%; (b) NIS, $AgNO_3$, Me_2CO, 23 °C, 91%; (c) **24**, Zn, DMF, 0 °C; CuCN, LiCl, THF, DMF, −40 → 23 °C; add **23**, −40 → 23 °C, 54% (d) Lawesson's Rgt, THF, 0 °C, 94%; (e) MeI, K_2CO_3, THF, 23 °C, 95%; (f) **14** (2 equiv), $(CH_2Cl)_2$, 23 °C, 65%; (g) NH_4F, MeOH, 23 °C, 79%; (h) $AuCl_3$, MeCN, 40 °C, 78%; (i) *p*-TsOH·H_2O, MeCN, 23 °C, 77%; (j) $Pd(PPh_3)_4$, pyrrolidine, MeCN, 23 °C, 81%; (k) Cs_2CO_3, DMF, 23 °C, 88%; (l) HCl, Et_2O, 0 °C, 77%.