Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2014, **5**, 2407

5-(Methylthio)tetrazoles as versatile synthons in the stereoselective synthesis of polycyclic pyrazolines *via* photoinduced intramolecular nitrile imine–alkene 1,3-dipolar cycloaddition†

Daniel Pla,*[a] Derek S. Tan*[ab] and David Y. Gin‡[ab]

Received 10th January 2014
Accepted 10th March 2014

DOI: 10.1039/c4sc00107a

www.rsc.org/chemicalscience

A key thioether substituent in readily accessible 2-alkyl-5-(methylthio)tetrazoles enables facile photoinduced denitrogenation and intramolecular nitrile imine 1,3-dipolar cycloaddition to afford a wide range of polycyclic pyrazoline products with excellent diastereoselectivity. The methylthio group red-shifts the UV absorbance of the tetrazole, obviating the requirement in all previous substrate systems for at least one aryl substituent, and can subsequently be converted into a variety of other functionalities. This synthetic platform has been applied to the concise total syntheses of the alkaloid natural products (±)-newbouldine and withasomnine.

Introduction

Pyrazolines and pyrazoles have demonstrated a broad range of biological activities, including antimicrobial, antiviral, analgesic, anti-inflammatory, anti-depressant, anticonvulsant, and anticancer properties.[1] 1,3-Dipolar cycloaddition of nitrile imines with alkenes and alkynes provides a powerful entry into this class of structures, with concurrent formation of C–C and C–N bonds (carboamination).[2] In pioneering work on this transformation, Huisgen demonstrated that the requisite nitrile imines could be generated *in situ* by basic elimination of α-halohydrazones[3] or by thermal[3a] or photoinduced denitrogenation of tetrazoles.[4] Subsequently, a variety of intramolecular variants have been described to afford polycyclic products.[5,6] More recently, Lin has reported photodenitrogenation under milder conditions that are useful for biological applications ('photoclick' reaction).[7]

Notably, however, in all of these reactions, the nitrile imine has at least one aryl substituent (*N*, *C*, or both); cycloaddition reactions of non-aromatic nitrile imines have apparently not been investigated previously,[8] and it has been suggested that an *N*-aryl substituent is absolutely required for reactivity in the tetrazole photodenitrogenation route to nitrile imines.[7c] To address this significant limitation in scope, we envisioned that a *C*-heteroatom substituent might enable the use of non-aryl substituted tetrazoles in the photoinduced pathway by red-shifting the absorbance of the substrate. We report herein efficient, stereoselective, photoinduced, intramolecular dipolar cycloadditions of readily accessible 2-alkyl-5-(methylthio)tetrazoles that afford a wide range of polycyclic pyrazolines. The *C*-methylthio group is proposed to facilitate the initial photodenitrogenation step and also provides a versatile handle for further functionalization, as demonstrated by application to the total syntheses of the alkaloid natural products (±)-newbouldine and withasomnine.

Results and discussion

Synthesis of tetrazole substrates

Our general approach involves regioselective alkylation of 5-(methylthio)tetrazole at the 2 position, followed by photoinduced denitrogenation and intramolecular 1,3-dipolar cycloaddition (Fig. 1). Due to the tautomerism exhibited by tetrazoles between their 1*H* and 2*H* forms, alkylation of **1** with alkyl bromides afforded a 45 : 55 mixture of 1- and 2-alkylated

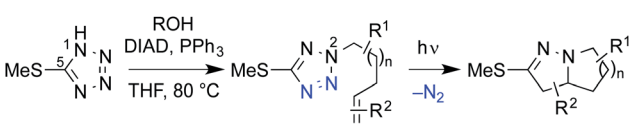


Fig. 1 General approach to photoinduced intramolecular dipolar cycloaddition of 2-alkyl-5-(methylthio)tetrazoles (**2**) not requiring *N*- or *C*-aryl substituents.

[a]*Molecular Pharmacology and Chemistry Program, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065, USA. E-mail: tand@mskcc.org; daniel.pla@gmail.com*

[b]*Tri-Institutional Research Program, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10065, USA*

† Electronic supplementary information (ESI) available: Complete experimental procedures and analytical data for all new compounds. See DOI: 10.1039/c4sc00107a

‡ Deceased, March 22, 2011.

products.[9] In contrast, Mitsunobu alkylation with alcohols proceeded with high regioselectivity for the desired 2-alkylated tetrazoles **2**.[10]

Initial studies of photoinduced intramolecular cycloaddition

We first investigated photoinduced denitrogenation and intramolecular cycloaddition of **2a** (Table 1). Although initial studies with a low-wattage Pen-Ray mercury lamp (5.5 W, 254 nm) appeared promising, low yields (<40% conversion, NMR) of **3a** were obtained even with extended reaction times (entries 1 and 2). In contrast, significantly higher yields were obtained upon irradiation for 5 h in a photoreactor (10 × 7.2 W low-pressure mercury lamps, 254 nm) (entry 3). Despite incomplete conversion under these conditions, longer irradiation times (8 h) did not result in improved yields (entry 4), and extended irradiation for 16 h led to complete *S*-demethylation to afford only thiopyrazolidinone byproduct **4a** (entry 5). Freeze–pump–thaw degassing of reactions had little influence on yield, and the reaction could be carried out conveniently under Ar or air atmosphere with similar efficiencies (entries 6 and 7), while reactions in other solvents resulted in slightly decreased yields (entries 8 and 9). Overall, reaction in CH_3CN under Ar atmosphere at rt for 5 h proved optimal, allowing consumption of ≈65–70% of the starting material with little or no *S*-demethylation to afford the highest overall yield of **3a** (entry 6).

Scope of photoinduced intramolecular cycloaddition

With these results in hand, we evaluated the effectiveness of this reaction across a wider range of substrates, synthesized *via* Mitsunobu alkylation with the corresponding alcohols.[11] Replacement of the 5-methylthio group with a 5-benzylthio group in **5** provided benzylthiopyrazoline **6** in similar yield (Table 2, entry 1). The reaction also accommodated formation of 3-, 6-, and 7-membered rings in **3b**, **3d**, and **3e**, but not of 4- or 8-membered rings in **3c** and **3f** (entries 2–6). The inaccessibility of **3c** and **3f** and decreased yields of **3d** and **3e** appeared to be due to competing quasi-dimerization side reactions.[11] Along similar lines, Padwa has reported that attempted 3- and 4-membered ring forming photoinduced cycloadditions with the corresponding 5-phenyltetrazole substrates result only in polymeric byproducts.[6i]

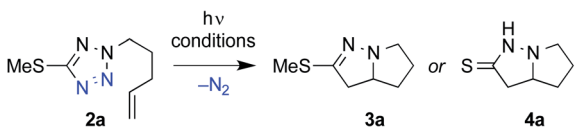
Both *E* and *Z*-disubstituted olefins in **2g** and **2h** were effective dipolarophiles, forming **3g** and **3h**, respectively (entries 7 and 8). While the incomplete diastereoselectivity in **3g** can be attributed to the presence of a small amount of the *Z*-isomer in the starting material **2g**, the incomplete diastereoselectivity in **3h** appears to be due to *in situ* photoinduced olefin isomerization of the substrate **2h** during the reaction (*vide infra*).[11] A vinylcyclopropane dipolarophile in **2i** also reacted effectively to form the intact cyclopropane-substituted pyrazoline **3i** (entry 9), consistent with a concerted reaction mechanism.[12] 1,1-Disubstituted and 1,2,2-trisubstituted olefins in **2j** and **2k** were also accommodated to form, respectively, **3j** having a methyl substituent at the bridgehead carbon and **3k** having a *gem*-dimethyl group on the pyrazoline ring (entries 10 and 11). A styrene dipolarophile in **2l** provided the corresponding pyrazoloisoindole tricycle **3l** (entry 12).

We next investigated branched substrates to assess the influence of various substituents on reaction efficiency and diastereoselectivity (Table 3). Introduction of a methyl substituent α to the tetrazole in **2m** favored formation of **3m** having a *syn* relationship between the methyl group and the bridgehead proton in good diastereoselectivity (entry 1). 1,1-Disubstituted and 1,2,2-trisubstituted olefins were again well-tolerated in **3n** and **3o** of this series (entries 2 and 3). In contrast, incorporation of a methyl substituent β to the tetrazole in **2p** favored the *anti* product **3p** (entry 4), with the methyl substituent presumably adopting an equatorial orientation on the otherwise sterically congested concave face of the ring system.[11] When the methyl substituent was shifted γ to the tetrazole in **2q**, the diastereopreference reverted back to the *syn* product **3q** (entry 5).

Introduction of a cyclic constraint between the γ- and δ-carbons in **2r** afforded the spirotricycle **3r** as a single diastereomer (entry 6), consistent with the diastereopreference observed above for **3q** (entry 5). Meanwhile, installation of a cyclic constraint between the α- and β-carbons in **2s** led to the fused tricycle **3s** with somewhat decreased diastereoselectivity (entry 7), as might be expected based on the opposing diastereopreferences above for **3n** and **3p** (entries 2 and 4). Moving to six-membered ring closures, high diastereoselectivity was achieved with cyclic constraints bridging the β- and γ-positions in reactions of **2t**, **2u**, and **2v** to form **3t**, **3u**, and **3v**, respectively (entries 8–10). Notably, the tertiary amine functionality was well-tolerated, providing access to pharmaceutically relevant piperidine and indole motifs.

Next, we investigated substrates having various alternative dipolarophiles (Table 4). An allyl ether in **2w** was accommodated readily to form pyrazolomorpholine **3w** (entry 1). Meanwhile, reaction of vinyl ether **2x** afforded pyrazole derivative **7**, presumably *via* initial formation of the corresponding pyrazolooxazolidine **3x** (not shown) followed by aromatization

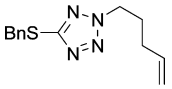
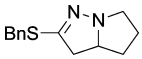
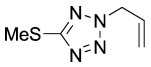
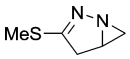
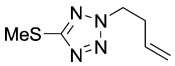
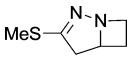
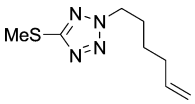
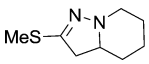
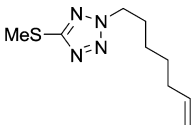
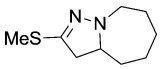
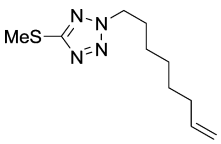
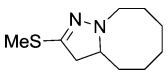
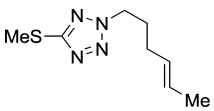
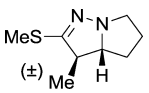
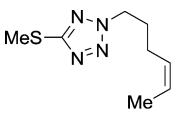
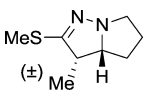
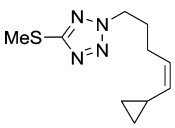
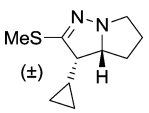
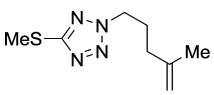
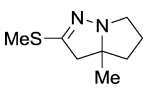
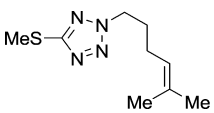
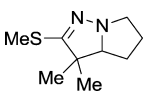
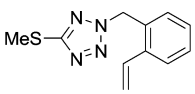
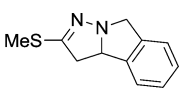
Table 1 Optimization of photoactivated intramolecular cycloaddition of **3a**[a]



Entry	Method[a]	Solvent	Conditions[b]	*t* (h)	Yield[c] **3a** (%)
1	A	CD_3CN	Air, rt	16	24
2	A	CH_3CN	Ar, rt	5	40
3	B	CH_3CN	Ar (FPT), rt	5	57
4	B	CH_3CN	Ar (FPT), rt	8	59
5	B	CH_3CN	Ar (FPT), rt	16	31 [**4a**]
6	B	CH_3CN	Ar, rt	5	64
7	B	CH_3CN	Air, rt	5	60
8	B	MeOH	Ar, rt	5	51
9	B	Acetone	Ar, rt	5	55

[a] Method A: Pen-Ray 5.5 W 254 nm lamp; method B: Luzchem 10 × 7.2 W 254 nm photoreactor. [b] FPT = freeze–pump–thaw degassed three times. [c] Isolated yields; majority of mass balance is **2a**.

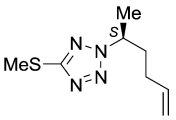
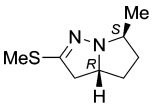
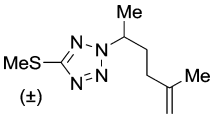
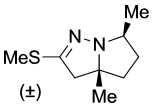
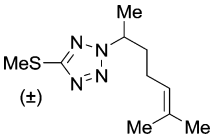
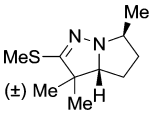
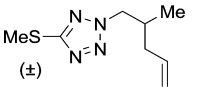
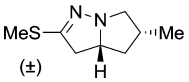
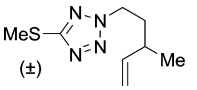
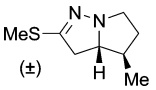
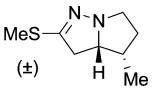
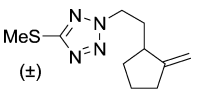
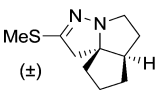
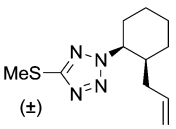
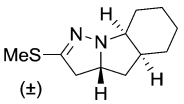
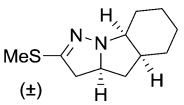
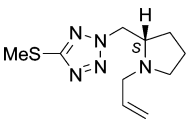
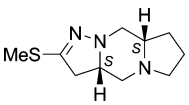
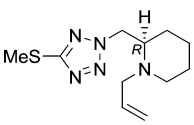
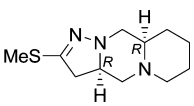
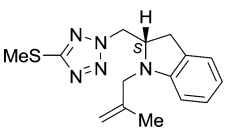
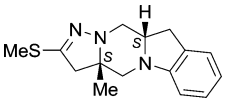
Table 2 Photoactivated intramolecular cycloadditions of substrates with varied ring sizes and alkene substitution[a,b]

Entry	Substrate	Yield (%)	Product	Yield (%)
1		**5:** 73		**6:** 65
2		**2b:** 56		**3b:** 68
3		**2c:** 77		**3c:** 0[c]
4		**2d:** 79		**3d:** 56[c]
5		**2e:** 77		**3e:** 35[c]
6		**2f:** 77		**3f:** 0[c]
7		**2g:** 75 (96 : 4 *E*/*Z*)		**3g:** 64[d] (19 : 1 dr)
8		**2h:** 81 (>99 : 1 *Z*/*E*)		**3h:** 62[d] (19 : 1 dr)
9		**2i:** 72 (94 : 6) *Z*/*E*		**3i:** 61[d] (18 : 2 dr)
10		**2j:** 76		**3j:** 70
11		**2k:** 77		**3k:** 67
12		**2l:** 65		**3l:** 70

[a] *hν* (254 nm, Luzchem 10 × 7.2 W lamp photoreactor), CH_3CN, Ar, rt, 5 h. [b] Relative stereochemistries determined by NOESY analysis.[11] [c] Remainder quasi-dimeric products, see Fig. SI4. [d] Isolated yield of inseparable mixture of diastereomers.

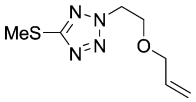
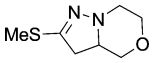
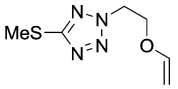
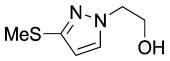
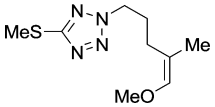
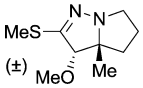
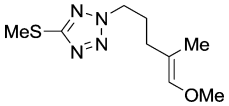
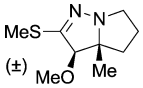
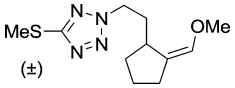
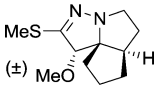
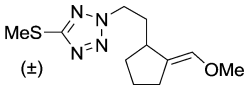
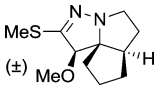
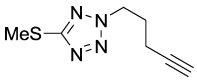
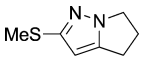
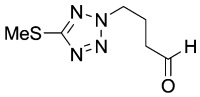
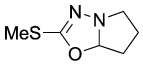
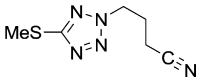
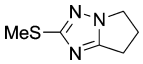
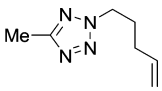
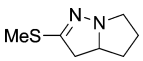
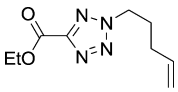
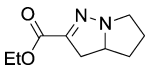
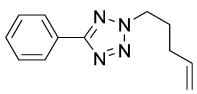
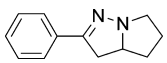
via elimination across the hemiaminal moiety (entry 2).[11] Enol ethers with the oxygen positioned at the distal end of the double bond were also accommodated effectively in **2y**, **2z**, **2aa**, and **2bb** to form **3y**, **3z**, **3aa**, and **3bb**, respectively (entries 3–6). The incomplete diastereoselectivity of these reactions is attributed to olefin isomerization in the substrates under the photochemical reaction conditions, which was observed in the remaining starting materials after the 5 h reaction time (**2aa** < 1 : 99 → 36 : 64 *E*/*Z* at 65% conversion; **2bb** > 99 : 1 → 92 : 8 *E*/*Z* at 56% conversion).[11] These ratios, combined with the observed diastereomeric ratios of the products, suggest that the *Z*-olefin substrate **2aa** reacts faster than the *E*-olefin substrate **2bb**.

Table 3 Photoactivated intramolecular cycloadditions of substrates with substituted linkers[a,b]

Entry	Substrate	Yield (%)	Product	Yield (%)
1		**2m:** 83		**3m:** 76[c] (17 : 3 dr)
2		**2n:** 72		**3n:** 72[c] (18 : 2 dr)
3		**2o:** 88		**3o:** 75[c] (16 : 4 dr)
4		**2p:** 78		**3p:** 72[c] (16 : 4 dr)
5		**2q:** 75		**3q:** 61[d] (16 : 4 dr)
				**3q′:** 15[d]
6		**2r:** 77		**3r:** 77[d] (>20 : 1 dr)
7		**2s:** 70		**3s:** 69[d] (15 : 5 dr)
				**3s′:** 27[d]
8		**2t:** 71		**3t:** 63[d] (>20 : 1 dr)
9		**2u:** 39		**3u:** 61[d] (19 : 1 dr)
10		**2v:** 76		**3v:** 42[c] (18 : 2 dr)

[a] *hν* (254 nm, Luzchem 10 × 7.2 W lamp photoreactor), CH_3CN, Ar, rt, 5 h. [b] Relative stereochemistries determined by NOESY analysis.[11] [c] Isolated yield of inseparable mixture of diastereomers. [d] Isolated yield of individual diastereomer shown.

Table 4 Photoactivated intramolecular cycloadditions of substrates with alternative dipolarophiles and tetrazole C5-substituents[a,b]

Entry	Substrate	Yield (%)	Product	Yield (%)
1		**2w**: 81		**3w**: 70
2		**2x**: 78		**7**: 72
3		**2y**: 86[c] (95 : 5 *Z*/*E*)		**3y**: 70[f] (18 : 2 dr)
4		**2z**: 85[c] (97 : 3 *E*/*Z*)		**3z**: 66[f] (15 : 5 dr)
5		**2aa**: 94[d] (>99 : 1) *Z*/*E*		**3aa**: 62[g] (18 : 2 dr)
6		**2bb**: 86[d] (>99 : 1) *E*/*Z*		**3bb**: 43[g] (17 : 3 dr)
7		**2cc**: 84		**8**: 19[h]
8		**2dd**: 71[e]		**9**: 0[i]
9		**2ee**: 72		**10**: 0[j]
10		**11**: 66		**12**: 0[k]
11		**13**: 45		**14**: 68
12		**15**: 91		**16**: 89

[a] *hν* (254 nm, Luzchem 10 × 7.2 W lamp photoreactor), CH_3CN, Ar, rt, 5 h. [b] Relative stereochemistry determined by NOESY analysis.[11] [c] Based on theoretical maximum yield from 37 : 63 *Z*/*E* ratio of alcohol precursor. [d] Based on theoretical maximum yield from 50 : 50 *Z*/*E* ratio of alcohol precursor. [e] Two-step yield from 4-hydroxybutyraldehyde dimethyl acetal precursor after acetal deprotection ($LiBF_4$, 2% H_2O in CH_3CN, rt, 20 h). [f] Isolated yield of inseparable mixture of diastereomers. [g] Isolated yield of major diastereomer. [h] Remainder unreacted starting material (major) and additional unidentified byproducts. [i] Complex mixture recovered. [j] Quasi-dimer recovered.[11] [k] Unreacted starting material recovered after 5 and 10 h irradiation.

Reaction with an alkyne dipolarophile in **2cc** proved sluggish, providing a low yield of the pyrazole **8** (entry 7).[6a,b,i] Attempted hetero-dipolar cycloaddition with an aldehyde[3a] in **2dd** to form oxadiazole **9** afforded only a complex mixture while attempted use of a nitrile dipolarophile[3a] in **2ee** to form 1,2,4-triazole **10** yielded only an unidentified byproduct, possibly an unsymmetrical quasi-dimer (MS, NMR) (entries 8 and 9).

It was of particular interest to note that replacement of the 5-methylthio group with a simple 5-methyl substituent in tetrazole **11** rendered the substrate unreactive to photodenitrogenation, and only unreacted starting material was recovered upon irradiation (entry 10). However, the corresponding 5-(carboethoxy)tetrazole **13** did undergo effective photodenitrogenation and dipolar cycloaddition to afford

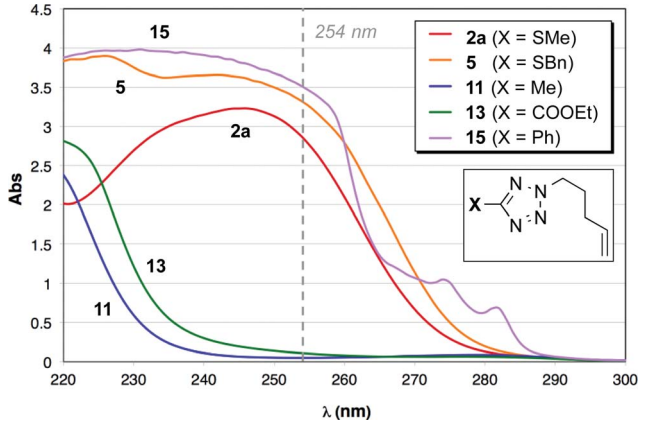


Fig. 2 UV absorbance spectra of 5-(methylthio)tetrazole **2a** (ε_{254} = 2520 M^{-1} cm^{-1}), 5-(benzylthio)tetrazole **5** (ε_{254} = 3080 M^{-1} cm^{-1}), 5-methyltetrazole **11** (ε_{254} = 4.89 M^{-1} cm^{-1}), 5-(carboethoxy)tetrazole **13** (ε_{254} = 72.6 M^{-1} cm^{-1}), and 5-phenyltetrazole **15** (ε_{254} = 8670 M^{-1} cm^{-1}) at 1.25 mM concentration in EtOH.[11] ε_{254} values were calculated based on spectra for which 0.1 < A_{254} < 3.0, the linear range of the instrument.[11]

pyrazoline ester **14** (entry 11). Similarly, the 5-phenyltetrazole **15** was efficiently converted to phenylpyrazoline **16** (entry 12), as reported previously by Padwa.[6i]

UV absorbance of 5-substituted tetrazoles

These last results highlight the importance of the 5-methylthio group in enabling the initial photodenitrogenation reaction, and suggest that the previous restriction of this reaction to aryl-substituted tetrazoles is due, at least in the case of photoactivated reactions, to the need for substrate absorbance in the medium-wave UV domain. Thus, we analyzed UV spectra of 5-(methylthio)tetrazole **2a**, 5-(benzylthio)tetrazole **5**, 5-methyltetrazole **11**, 5-(carboethoxy)tetrazole **13**, and 5-phenyltetrazole **15** (Fig. 2). The 5-thiotetrazoles **2a** and **5** absorbed strongly at 254 nm, nearly as well as the 5-phenyltetrazole **15**. In contrast, the 5-methyltetrazole **11** absorbed very weakly at this wavelength. This is consistent with the hypothesis that the phenyl and thiomethyl substituents facilitate the initial photodenitrogenation reaction by increasing the UV absorbance of the substrates at 254 nm. Notably, however, 5-(carboethoxy)tetrazole **13** absorbed relatively weakly at this wavelength, despite its effectiveness in the photoinduced cycloaddition reaction (Table 4, entry 11). Thus, these tetrazole substituents may also play a role in increasing substrate reactivity by electronic stabilization of the corresponding nitrile imine intermediates.[13]

Further functionalization of pyrazoline scaffolds

The (methylthio)pyrazoline products of these photoinduced cycloaddition reactions proved to be versatile scaffolds that underwent a variety of downstream transformations (Fig. 3). Oxidation of **3a** with DDQ under microwave irradiation provided rapid, efficient access to the corresponding pyrazole **8**,[6i] which could not be accessed efficiently by direct cycloaddition of alkyne **2cc** above (Table 4, entry 7). Palladium-catalyzed

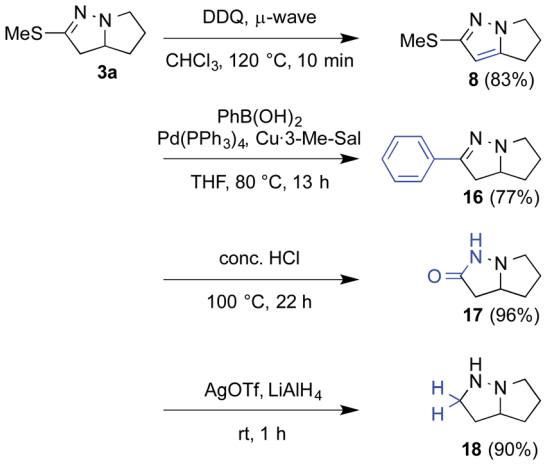


Fig. 3 Downstream transformations of pyrazoline **3a**. (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; 3-Me-Sal = 3-methyl.)

Liebskind–Srogl cross-coupling[14] of the thioimidate with phenylboronic acid also provided phenyl-substituted pyrazoline **16**. While such aryl-substituted scaffolds could, of course, be synthesized directly by photoinduced cycloaddition of appropriate 2-alkyl-5-aryltetrazoles (*e.g.*, **15** → **16**, Table 4, entry 12), the commercial availability of a wide range of boronic acids makes this alternative, divergent approach highly attractive. The thioimidate moiety could also be hydrolyzed efficiently to the cyclic hydrazide **17**. Such pyrazolidinones can undergo *N*–*N*-bond cleavage to prepare β-homoproline amide derivatives,[15] for use in β-peptides.[16] A novel desulfurizative reduction of **3a** in the presence of AgOTf also provided direct entry to the corresponding pyrazolidine **18**.

Total synthesis of (±)-newbouline and withasomnine

To demonstrate further the utility of photoinduced nitrile imine cycloadditions of 2-alkyl-5-(methylthio)tetrazoles, we applied this synthetic platform to the total syntheses of (±)-newbouldine (**19**) and withasomnine (**20**, Fig. 4). This family of pyrrolopyrazole alkaloids was isolated from plant sources[17,18] that are used in traditional medicines for a wide range of indications.[19] Several syntheses of the achiral pyrazole congener withasomnine have been reported, most of which start from a pyrazole or pyrrolidine scaffold with cyclization of a sidechain to install the second ring.[20,21] In contrast, the first synthesis of

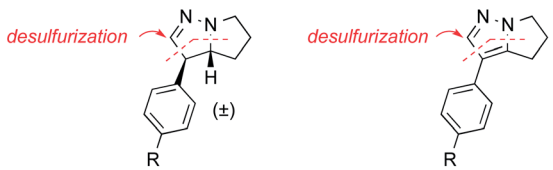


Fig. 4 Structures of the newbouldine and withasomnine alkaloid families and retrosynthetic disconnections.

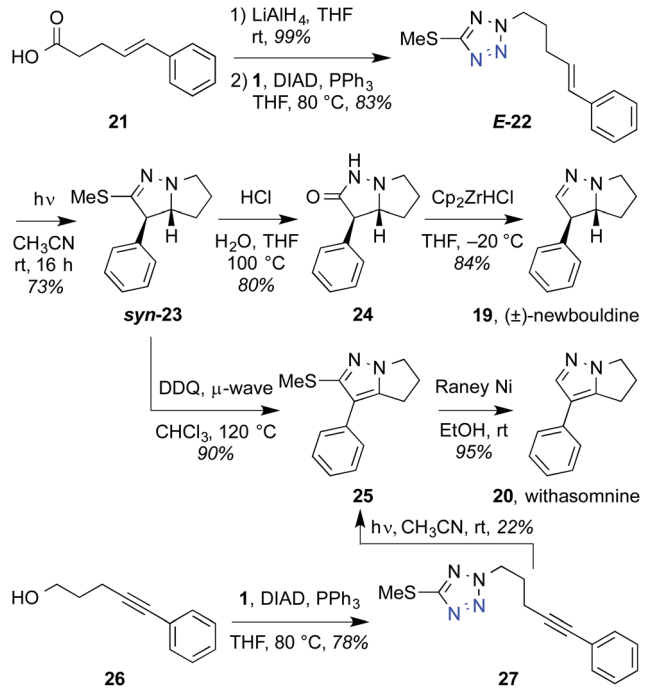


Fig. 5 Total synthesis of newbouldine and withasomnine *via* photoinduced intramolecular nitrile imine cycloaddition of 2-alkyl-5-(methylthio)tetrazole ***E*-22**.

the pyrazoline congener (−)-newbouldine was reported only recently by Trauner, using reductive cyclization of a nitroalkyl-substituted pyrrolidine and confirming the racemic nature of this natural product.[22]

Thus, we synthesized the tetrazole substrate ***E*-22** by $LiAlH_4$ reduction of acid **21** (ref. 23) followed by Mitsunobu reaction of the resulting alcohol with 5-(methylthio)tetrazole (**1**) (Fig. 5).[10] Photoinduced intramolecular nitrile imine cycloaddition of ***E*-22** proceeded efficiently to the pyrrolopyrazoline ***syn*-23**, albeit requiring an extended 16 h reaction time for consumption of all starting material. The crude product was obtained in 18 : 2 dr and the major diasteromer ***syn*-23** was isolated in 73% yield. As

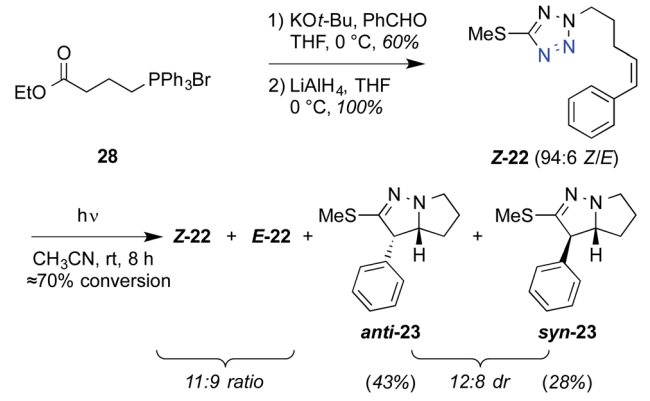


Fig. 6 Photoinduced intramolecular cycloaddition of *Z*-olefin ***Z*-22** results in a mixture of ***anti*-23** and ***syn*-23** with *E*/*Z* isomerization of remaining starting material (***Z*/*E*-22**).

above (Table 1, entries 7, 8, and Table 4, entries 5, 6), this diastereomeric mixture is attributed to *in situ* olefin isomerization of the substrate under the photochemical reaction conditions, which was observed in the remaining starting material **22** after 8 h reaction time (97 : 3 → 95 : 5 *E*/*Z*). Similarly, photoinduced cycloaddition of the corresponding *Z*-olefin substrate ***Z*-22** afforded a mixture of the corresponding *anti*-3,4 pyrrolopyrazoline ***anti*-23** and ***syn*-23**, with olefin isomerization observed in the remaining starting materials (Fig. 6).[11]

Attempts to desulfurize ***syn*-23** directly to newbouline using Raney Ni and Raney Cu resulted in decomposition and recovery of unreacted starting material, respectively. Desulfurization of the model substrate **3a** was also attempted under a variety of conditions and resulted in either no reaction (Al·Hg; NiB; H_2, $Pd(OH)_2/C$; $LiAlH_4$; Raney Cu; Et_3SiH, Pd/C; Bu_3SnH, $CuBr\cdot SMe_2$, $Pd(PPh_3)_4$) or decomposition ($BH_3\cdot THF$; $LiBHEt_3$). However, a two-step procedure involving initial hydrolysis of ***syn*-23** to pyrazolidinone **24** followed by selective hydrazide-to-hydrazone reduction with Schwartz's reagent[24] afforded (±)-newbouldine (**19**) in five steps and 40% overall yield from acid **21**.

In initial efforts to access withasomnine (**20**), an analogous alkynyl tetrazole substrate **27** underwent sluggish photoinduced cycloaddition to pyrrolopyrazole **25** in 22% yield (Fig. 5), consistent with the reduced reactivity observed above for alkyne substrate **2cc** (Table 4, entry 7). In contrast, the same pyrazole **25** could be accessed more efficiently by DDQ oxidation[6i] of the alkene-derived pyrazoline ***syn*-23**. Subsequent desulfurization with Raney Ni provided withasomnine (**20**) in five steps and 51% overall yield from acid **21**.

Conclusions

Nitrile imine cycloadditions were first described by Huisgen over 50 years ago[3,4] and provide rapid access to functionalized pyrazoline scaffolds found in diverse biologically active molecules. However, to date, these reactions have apparently been restricted in scope to nitrile imines having at least one aryl substituent, regardless of whether the nitrile imines are generated photochemically or thermally from tetrazoles, or *via* basic elimination of α-halohydrazones. Thus, these aryl substituents may play a role in stabilizing the reactive nitrile imine intermediates to decrease kinetic barriers and/or avoid undesired rearrangement side reactions.[13] In the case of photoinduced reactions involving initial denitrogenation of tetrazoles, UV analysis of substrates having differential reactivities herein (Fig. 2) suggests an additional role of such aryl substituents in facilitating the initial photodenitrogenation step by increasing the UV_{254} absorbance of the substrates. Importantly, we have found that introduction of a heteroatom substituent allows tetrazole photodenitrogenation and intramolecular nitrile imine cycloaddition to proceed under mild conditions. The reaction tolerates a wide range of substituent patterns and is diastereoselective, although photochemical olefin isomerization can be limiting for certain substrates. Further, this versatile 5-methylthio group can subsequently be converted to a variety of other functionalities. Indeed, the utility

of this 5-(methylthio)tetrazole platform has been demonstrated by application to the concise total syntheses of the pyrrolopyrazole alkaloids (±)-newbouline and withasomnine. The finding that the photoinduced cycloaddition can also be potentiated by other, non-aryl substituents such as esters (Table 4, entry 11) opens the door to investigation of other such substituents in the future.

Acknowledgements

Dedicated to the memory of our esteemed colleague and mentor, Prof. David Y. Gin (1967–2011). We thank Dr William Walkowicz (MSKCC) for assistance with UV spectra and Dr George Sukenick, Dr Hui Liu, Hui Fang, and Dr Sylvia Rusli (MSKCC Analytical Core Facility) for expert NMR and mass spectral support. Financial support from the NIH (GM067659 to D. Y. G.) and an European Commission Marie Curie International Outgoing Fellowship under the 7th Framework Programme (FP7-PEOPLE-2009-IOF-253205 to D. P.) is gratefully acknowledged.

Notes and references

1 (*a*) X.-H. Liu, B.-F. Ruan, J. Li, F.-H. Chen, B.-A. Song, H.-L. Zhu, P. S. Bhadury and J. Zhao, *Mini-Rev. Med. Chem.*, 2011, **11**, 771–821; (*b*) M. A. Rahman and A. A. Siddiqui, *Int. J. Pharm. Sci. Drug Res.*, 2010, **2**, 165–175; (*c*) S. Kumar, S. Bawa, S. Drabu, R. Kumar and H. Gupta, *Recent Pat. Anti-Infect. Drug Discovery*, 2009, **4**, 154–163; (*d*) A. Schmidt and A. Dreger, *Curr. Org. Chem.*, 2011, **15**, 1423–1463.

2 (*a*) J. T. Sharp, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, ed. A. Padwa and W. H. Pearson, Wiley, New York, 2002, ch. 7, pp. 473–537; (*b*) P. Caramella and P. Gruenanger, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, ch. 3, vol. 1, pp. 291–392.

3 (*a*) R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland and G. Wallbillich, *J. Org. Chem.*, 1959, **24**, 892–893; (*b*) R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, 1962, **17**, 3–29; (*c*) R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich and V. Weberndoerfer, *Chem. Ber.*, 1967, **100**, 1580–1592; (*d*) W. Fliege, R. Grashey and R. Huisgen, *Chem. Ber.*, 1984, **117**, 1194–1214.

4 (*a*) J. S. Clovis, A. Eckell, R. Huisgen and R. Sustmann, *Chem. Ber.*, 1967, **100**, 60–70; (*b*) W. Fliege, R. Huisgen, J. S. Clovis and H. Knupfer, *Chem. Ber.*, 1983, **116**, 3039–3061; (*c*) J. S. Clovis, W. Fliege and R. Huisgen, *Chem. Ber.*, 1983, **116**, 3062–3070.

5 (*a*) G. Broggini, G. Molteni and G. Zecchi, *Heterocycles*, 1998, **47**, 541–557; (*b*) A. Padwa, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, ch. 12, vol. 2, pp. 277–406.

6 (*a*) R. Fusco, L. Garanti and G. Zecchi, *Tetrahedron Lett.*, 1974, 269–272; (*b*) L. Garanti and G. Zecchi, *Synthesis*, 1974, 814–815; (*c*) L. Garanti, A. Sala and G. Zecchi, *Synthesis*, 1975, 666–669; (*d*) L. Garanti, A. Sala and G. Zecchi, *Synth. Commun.*, 1976, **6**, 269–275; (*e*) L. Garanti, A. Locatelli and G. Zecchi, *J. Heterocycl. Chem.*, 1976, **13**, 657–659; (*f*) L. Garanti, A. Sala and G. Zecchi, *J. Org. Chem.*, 1977, **42**, 1389–1392; (*g*) H. Meier, H. Heimgartner and H. Schmid, *Helv. Chim. Acta*, 1977, **60**, 1087–1090; (*h*) H. Meier and H. Heimgartner, *Helv. Chim. Acta*, 1977, **60**, 3035–3038; (*i*) A. Padwa, S. Nahm and E. Sato, *J. Org. Chem.*, 1978, **43**, 1664–1671; (*j*) E. Sato, Y. Kanaoka and A. Padwa, *J. Org. Chem.*, 1982, **47**, 4256–4260; (*k*) G. Schmitt and B. Laude, *Tetrahedron Lett.*, 1978, 3727–3728.

7 (*a*) R. K. V. Lim and Q. Lin, *Acc. Chem. Res.*, 2011, **44**, 828–839; (*b*) Y. Wang, C. I. Rivera Vera and Q. Lin, *Org. Lett.*, 2007, **9**, 4155–4158; (*c*) Y. Wang and Q. Lin, *Org. Lett.*, 2009, **11**, 3570–3573; (*d*) J. Wang, W. Zhang, W. Song, Y. Wang, Z. Yu, J. Li, M. Wu, L. Wang, J. Zang and Q. Lin, *J. Am. Chem. Soc.*, 2010, **132**, 14812–14818; (*e*) W. Song, Y. Wang, Z. Yu, C. I. R. Vera, J. Qu and Q. Lin, *ACS Chem. Biol.*, 2010, **5**, 875–885; (*f*) Z. Yu, L. Y. Ho and Q. Lin, *J. Am. Chem. Soc.*, 2011, **133**, 11912–11915.

8 Nucleophilic addition to an *N*-*t*-butyl-*C*-anilinoalkenyl nitrile imine intermediate has been proposed in an undesired side reaction observed during heating of the corresponding tetrazole (Ph_2O, 121 °C, 15 min, 15% yield): S. Isoda and H. Kanno, *Heterocycles*, 1992, **33**, 273–279.

9 R. J. Spear, *Aust. J. Chem.*, 1984, **37**, 2453–2468.

10 C. F. Purchase and A. D. White, *Synth. Commun.*, 1996, **26**, 2687–2694.

11 See ESI for full details.†

12 (*a*) R. D. Harcourt, *Tetrahedron*, 1978, **34**, 3125–3127; (*b*) R. D. Harcourt and R. D. Little, *J. Am. Chem. Soc.*, 1984, **106**, 41–46; (*c*) B. Braida, C. Walter, B. Engels and P. C. Hiberty, *J. Am. Chem. Soc.*, 2010, **132**, 7631–7637.

13 G. Bertrand and C. Wentrup, *Angew. Chem., Int. Ed.*, 1994, **33**, 527–545.

14 (*a*) H. Prokopcová and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2009, **48**, 2276–2286; (*b*) L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, 2000, **122**, 11260–11261; (*c*) J. M. Villalobos, J. Srogl and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2007, **129**, 15734–15735; (*d*) J. Schleiss, P. Rollin and A. Tatibouët, *Angew. Chem., Int. Ed.*, 2010, **49**, 577–580.

15 J.-G. Roveda, C. Clavette, A. D. Hunt, S. I. Gorelsky, C. J. Whipp and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2009, **131**, 8740–8741.

16 (*a*) R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219–3232; (*b*) S. Gobi, K. Knapp, E. Vass, Z. Majer, G. Magyarfalvi, M. Hollosi and G. Tarczay, *PCCP Phys. Chem. Chem. Phys.*, 2010, **12**, 13603–13615.

17 Withasomnine: (*a*) H. B. Schröter, D. Neumann, A. R. Katritzky and F. J. Swinbourne, *Tetrahedron*, 1966, **22**, 2895–2897; (*b*) P. Houghton, R. Pandey and J. E. Hawkes, *Phytochemistry*, 1994, **35**, 1602–1603.

18 Newbouldine: (*a*) S. A. Adesanya, R. Nia, C. Fontaine and M. Païs, *Phytochemistry*, 1994, **35**, 1053–1055; (*b*) A. J. Aladesanmi, R. Nia and A. Nahrstedt, *Planta Med.*, 1998, **64**, 90–91.

19 (*a*) P. Jayasinha, D. Warnasuriya and H. Dissanayake, *Ashwagandha (Withania somnifera)*, Information Services Centre, Industrial Technology Institute, Colombo, Sri Lanka, 1999, http://dl.nsf.ac.lk/handle/1/5419; (*b*)

A. Correira, A. Costa and M. Q. Paiva, *Ann. Fac. Farm. Porto*, 1965, **25**, 35–50; (*c*) H. M. Burkhill, *The Useful Plants of West Tropical Africa*, Royal Botanical Gardens, Kew, London, 1985, vol. 1, 2 edn, pp. 259–262; (*d*) F. R. Irvine, *Woody Plants of Ghana, with Special Reference to their Uses*, Oxford University Press, London, 1961.

20 (*a*) A. Morimoto, K. Noda, T. Watanabe and H. Takasugi, *Tetrahedron Lett.*, 1968, 5707–5710; (*b*) T. Onaka, *Tetrahedron Lett.*, 1968, 5711–5714; (*c*) A. Zubek, *Pharmazie*, 1969, **24**, 382–384; (*d*) S. Takano, Y. Imamura and K. Ogasawara, *Heterocycles*, 1982, **19**, 1223–1225; (*e*) A. Guzman-Perez and L. A. Maldonado, *Synth. Commun.*, 1991, **21**, 1667–1674; (*f*) O. Kulinkovich, N. Masalov, V. Tyrorskii, N. De Kimpe and M. Keppens, *Tetrahedron Lett.*, 1996, **37**, 1095–1096; (*g*) S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2002, **43**, 4191–4193; (*h*) S. M. Allin, W. R. S. Barton, W. Russell Bowman, E. Bridge, M. R. J. Elsegood, T. McInally and V. McKee, *Tetrahedron*, 2008, **64**, 7745–7758; (*i*) S. Majumder, K. R. Gipson, R. J. Staples and A. L. Odom, *Adv. Synth. Catal.*, 2009, **351**, 2013–2023; (*j*) H. Ichikawa, R. Watanabe, Y. Fujino and Y. Usami, *Tetrahedron Lett.*, 2011, **52**, 4448–4451; (*k*) R. Kumar and I. N. N. Namboothiri, *Org. Lett.*, 2011, **13**, 4016–4019.

21 Intermolecular cycloadditions of mesoionic sydnone dipoles have also been used to construct the pyrazole ring: (*a*) D. Ranganathan and S. Bamezai, *Synth. Commun.*, 1985, **15**, 259–265; (*b*) D. Ranganathan, S. Bamezai, C. H. He and J. Clardy, *Tetrahedron Lett.*, 1985, **26**, 5739–5742; (*c*) D. Ranganathan, S. Bamezai and S. Saini, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1991, **30**, 169–175; (*d*) R. S. Foster, J. Huang, J. F. Vivat, D. L. Browne and J. P. A. Harrity, *Org. Biomol. Chem.*, 2009, **7**, 4052–4056.

22 M. Pangerl, C. C. Hughes and D. Trauner, *Tetrahedron*, 2010, **66**, 6626–6631.

23 S. E. Denmark and M. T. Burk, *Org. Lett.*, 2012, **14**, 256–259.

24 Zirconium(IV) salts have used previously to convert secondary amides and lactams to *N*-substituted imines in one step: (*a*) D. J. A. Schedler, J. Li and B. Ganem, *J. Org. Chem.*, 1996, **61**, 4115–4119; (*b*) M. A. Arnold, K. A. Day, S. G. Durón and D. Y. Gin, *J. Am. Chem. Soc.*, 2006, **128**, 13255–13260.