JOC The Journal of Organic Chemistry

Article

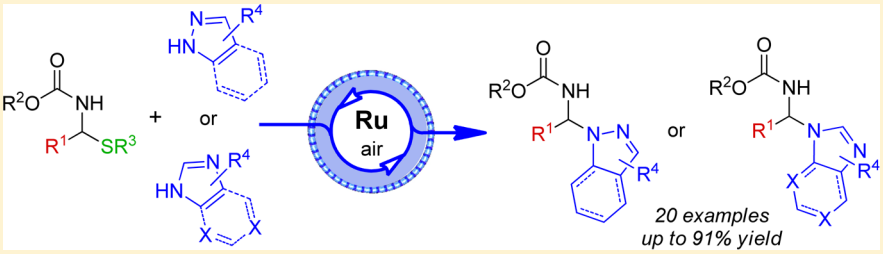
pubs.acs.org/joc

Visible-Light Photoredox-Catalyzed Coupling Reaction of Azoles with α-Carbamoyl Sulfides

Lucie Jarrige, Guillaume Levitre, and Géraldine Masson*

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1, av de la Terrasse, Gif-sur-Yvette 91198 Cedex, France

Supporting Information



ABSTRACT: A simple, straightforward strategy for the synthesis of *N*-substituted azoles is reported that involves a visible-light photoredox-catalyzed coupling reaction of azoles with α-carbamoyl sulfides. A variety of heterocyclic units, including pyrazoles, benzopyrazoles, benzoimidazoles, and purines, can be efficiently incorporated under mild reaction conditions in respectable yields.

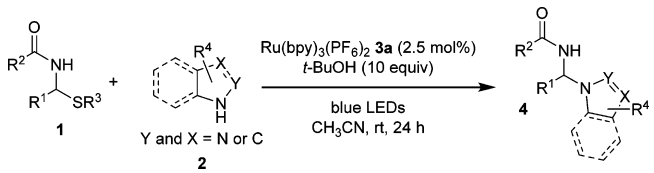
INTRODUCTION

Five-membered heterocycles containing nitrogen have attracted significant interest in organic and medicinal chemistry over the past several decades. Scaffolds containing a pyrazole[1] or imidazole[2] are found in a number of pharmaceutically and biologically active important molecules. Therefore, the development of efficient synthetic methods for these heterocycles is in high demand. Among the various methods available,[3−6] the incorporation of these valuable azoles into the α position of amines is certainly one of the most simple and direct approaches. However, despite a wide variety of easily available five-membered heterocycles, such strategies have been mentioned in the literature only briefly.[7] Recently, we have reported an efficient visible-light photoredox-catalyzed[8] addition of various aryl and heteroaryl to α-amido sulfides[9a−e] as *N*-carbamoylimine precursors[9] leading to the rapid generation of a range of functionalized *N*-protected aryl- or heteroarylamines.[10,11] In line with this work,[10,12] we envisioned that this method could be utilized to incorporate a wide range of aromatic 5-membered azacyclic units. This would lead to the formation of 2-(aminomethyl)azoles which are present in various bioactive molecules.[13] We report herein an efficient visible-light photoredox-catalyzed *N*-alkylation of azoles and fused azoles **2** into α-amido sulfides **1** leading to the rapid and efficient generation of a range of functionalized 2-(aminomethyl)azoles **4** (Scheme 1).

RESULTS AND DISCUSSION

We have already reported that the reaction of pyrazole (**2a**) and *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**) in the presence of 2.5 mol % of $Ru(bpy)_3(PF_6)_2$ photocatalyst **3a**

Scheme 1. Photoredox-Catalyzed Synthesis of *N*-Alkyl-Substituted Azoles



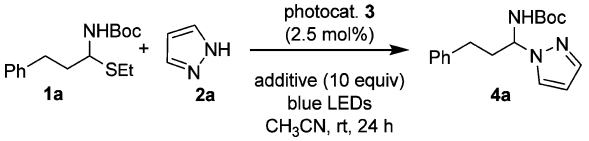
under visible-light irradiation (5 W blue LEDs) in dichloromethane/*t*-BuOH (8:2, v/v) at room temperature yielded the desired product **4a** in 70% yield after 24 h.[10] In previous works, mainly electron-rich aromatics were examined, and because of our interest in oxidative activation of the C−S bond adjacent to a nitrogen,[9c,10] we re-examined the photoredox *N*-alkylation reaction to expand their synthetic utility and gain additional insight into this visible-light photoredox process. Performance of the other photoredox catalysts, such as $Ru(bpy)_3Cl_2$, $Ru(bpz)_3Cl$, and eosin (Table 1 entries 2−4),[14] was inferior to that of $Ru(bpy)_3(PF_6)_2$. Yields were lower in the absence of *t*-BuOH (entry 7) or with hexafluoro-2-propanol or EtOH as the cosolvent (entries 8 and 9).[15] As already observed by us, the concentration of **1a** in the reaction is very important, and the use of 0.5 M in MeCN is the best concentration for a good yield. Any change in this concentration led to a drop of the yield (entries 5 and 6 vs 1). The reaction did not proceed at all

Special Issue: Photocatalysis

Received: May 11, 2016
Published: June 17, 2016

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230−7236

Table 1. Optimization of Reaction Conditions for the Synthesis of α-Carbamoylpyrazoles[a]



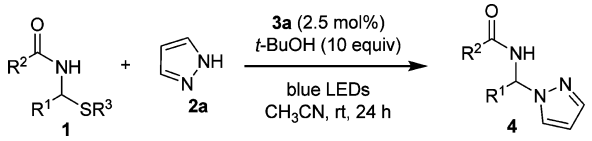
entry	3	additive	yield[b] (%)
1	$Ru(bpy)_3(PF_6)_2$ (**3a**)	*t*-BuOH	70
2	$Ru(bpy)_3Cl_2$ (**3b**)	*t*-BuOH	28
3	$Ru(bpz)_3Cl_2$ (**3c**)	*t*-BuOH	28
4	eosin Y (**3d**)	*t*-BuOH	41[c]
5	**3a**	*t*-BuOH	45[d]
6	**3a**	*t*-BuOH	50[e]
7	**3a**		28[e]
8	**3a**	HFIP	50
9	**3a**	EtOH	trace[f]
10	**3a**	*t*-BuOH	trace[g]
11	**3a**	*t*-BuOH	88[h]
12	**3a**	*t*-BuOH	19[i]
13	**3a**	*t*-BuOH	19[j]
14		*t*-BuOH	0[k]
15	**3a**	*t*-BuOH	0[k,l]
16	**3a**	*t*-BuOH	0[m]

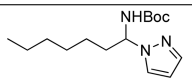
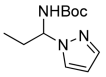
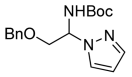
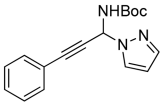
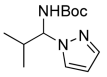
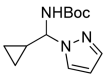
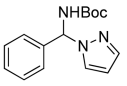
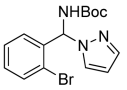
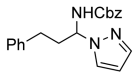
[a]General conditions: **1** (0.10 mmol), pyrazole **2a** (0.15 mmol), **3** (0.025 equiv), additive (10 equiv) in MeCN (0.5 mL) irradiated at rt for 24 h. [b]Yields refer to chromatographically pure product. [c]Irradiated with green LEDs. [d]MeCN (1 mL). [e]MeCN (2 mL). [f]α-Carbamoyl ether was isolated as the major product. [g]Oxygen-free conditions. [h]With air. [i]$BrCCl_3$ (0.025 mmol) was used as oxidative quencher. [j]Methyl viologen (0.025 mmol) was used as oxidative quencher. [k]Starting material was recovered. [l]Without any irradiation. [m]Under free oxygen.

in strict oxygen-free conditions (entry 10). In contrast, the yield of the product was increased to 88% (entry 11) when the reaction was carried out in the presence of air (open to air, without bubbling air). Moreover, no reaction proceeds in anaerobic conditions; only starting material was revovered (entry 16). These results indicated that the ruthenium complex undergoes oxidative quenching of its excited state with oxygen to give the strongly oxidizing $Ru(bpy)_3^{3+}$.[8] Other oxidative quenchers such as $BrCCl_3$[11] and methyl viologen were evaluated (entries 12 and 13), and the conclusion was that oxygen is superior to the other quenchers.

Then, with the optimized reaction conditions in hand, we examined the scope and limitations of the photoredox-catalyzed *N*-alkylation reaction. As shown in Table 2, various α-carbamoyl sulfides **1** were explored by using pyrazole (**2a**) as the reactant. The yields of *N*-alkylated products **4** resulting from aliphatic α-carbamoyl sulfides **1** were generally moderate to excellent. The photocatalytic system also proved to be efficient for various linear aliphatic α-carbamoyl sulfides **1b−c** leading to the coupling products (**4b−c**, entries 1−3) in good to excellent yields. We were pleased to find that the presence of functional groups such as benzyl ether (**4d**, entry 3) and alkyne (**4e**, entry 4)[16] was tolerated. The reaction between α-carbamoyl sulfides derived from β-branched aldehydes **1f** and **1g** with pyrazole **2a** under the same conditions afforded moderate to good yields of the corresponding *N*-alkylated products **4f** and **4g** (entries 5 and 6). The replacement of the Boc group **1a** with a Cbz group **1j** has no influence on the efficiency of the amidoalkylation (entry 9). In addition, the

Table 2. Reactions of Various α-Carbamoyl Sulfides 1 with Pyrazole 2a[a]



entry	R^1	Product	4	yield (%)[b]
1	C_6H_{13}		**4b**	87
2	C_2H_5		**4c**	61
3	C_8H_9O		**4d**	58
4	C_8H_5		**4e**	47[c]
5	C_3H_7		**4f**	75
6	C_3H_5		**4g**	41
7	C_6H_5		**4h**	45(60)[c]
8	C_6H_5		**4i**	66[c]
9	C_8H_9		**4j**	85

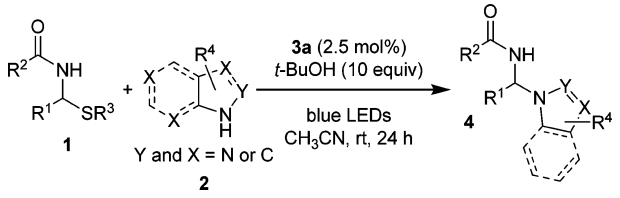
[a]Reaction conditions: **1** (0.10 mmol), pyrazole **2a** (0.15 mmol), **3a** (0.025 equiv), *t*-BuOH (10.0 equiv) in MeCN (0.5 mL) irradiated at rt for 24 h. [b]Yields refer to chromatographically pure product. [c]With 5 mol % of **3a**.

catalytic process can be applied to an aromatic α-amido sulfide such as **1h**, although the yield was slightly lower (entry 7). However, when the reaction was carried out with 5 mol % of $Ru(bpy)_3(PF_6)_2$ **3a** under otherwise identical conditions, the expected *N*-alkylated products **4h** and **4i** were isolated in better yields (entries 7 and 8).

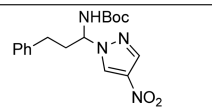
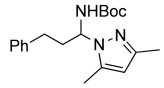
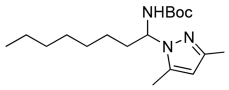
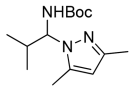
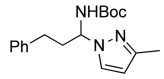
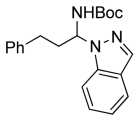
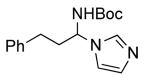
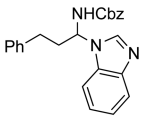
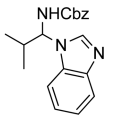
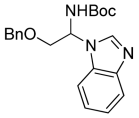
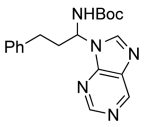
We next examined the coupling reaction of several azoles as well as fused azoles **2**. As shown in Table 3, the presence of an electron-donating group and an electron-withdrawing group on the pyrazole ring **2b−d** were found to be suitable substrates giving the corresponding *N*-alkyalted products **4k−o** (entries 1−5) in good yields. Interestingly, when the 3-methylpyrazole **2d** was employed, the photocatalyzed *N*-alkylation reaction led only to the formation of the less congested regioisomer **4o** (entry 5). Similarly, the reaction of aryl-fused pyrazoles such as benzopyrazole **2e** went very smoothly to afford **4p** in excellent yield (91% yield, entry 6). Unsubstituted imidazole **2f** provided

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230−7236

Table 3. Reactions of α-Carbamoyl Sulfides 1 with Various Azoles 2[a]



1 2 4

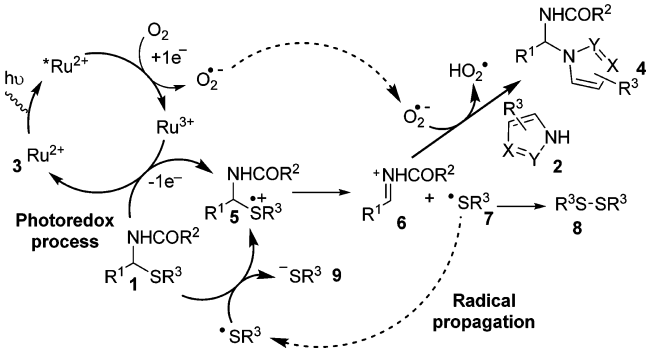
entry	R^1	Product	4	yield (%)[b]
1	C_8H_9		**4k**	66
2	C_8H_9		**4l**	79
3	C_7H_{15}		**4m**	59
4	C_8H_9		**4n**	75
5	C_3H_7		**4o**	86
6	C_8H_9		**4p**	91
7	C_8H_9		**4q**	21[c]
8	C_8H_9		**4r**	79
9	C_3H_7		**4s**	67
10	C_8H_9O		**4t**	74
11	C_8H_9		**4u**	81

[a]Reaction conditions: **1** (0.10 mmol), pyrazole **2** (0.15 mmol), **3a** (0.025 equiv), *t*-BuOH (10.0 equiv) in MeCN (0.5 mL) irradiated at rt for 24 h. [b]Yields refer to chromatographically pure product. [c]With 5 mol % of **3a**.

the corresponding coupling adducts **4q** in a low yield, even with 5 mol % of **3a** (entries 7). On the other hand, when the benzoimidazole **2g** was the nucleophile in the reaction, *N*-alkylated products (**4r**–**t**) were isolated in much better yields (entries 8–10). Most remarkably, the coupling reaction worked well with purine to afford an efficient access to azacyclic purine aza-nucleosides **4u** (entry 11).[7a]

The following control experiments were conducted to gain some mechanistic insight. No reaction took place in the absence of light and/or photocatalyst. Moreover, the formation of **4** was inhibited in the presence of radical scavengers such as TEMPO and galvinoxyl, suggesting that a radical/cationic process is involved in this reaction. Based on the literature[8,17,18] and our previous study,[10] we propose a plausible catalytic cycle for the present *N*-alkylation reaction as depicted in Scheme 2.

Scheme 2. Plausible Reaction Mechanism



First, Ru^{2+} is excited to $*Ru^{2+}$ under blue LED irradiation. Then, this excited state undergoes an oxidative quenching with oxygen molecule to give Ru^{3+} and superoxide radical anion ($O_2^{\bullet-}$). This strong oxidant Ru^{3+} is prone to activate α-carbamoyl sulfides **1** through an additional single-electron oxidation step causing the generation of radical cation **5** and regenerating the ground-state Ru^{2+} **3**. The resulting radical cation **5** may undergo a fragmentation to cleave the labile N–S bond and give the *N*-carbamoyliminium **6** as well as thiyl radical **7**. Unfortunately, all attempts to prove the formation of this radical were unsuccessful.[19] In parallel, the thiyl radical **7** is then proposed to dimerize to form disulfide **8**. A small amount of disulfide was isolated from this reaction, confirming our assumption.[10] However, an alternative pathway involving the conversion of α-carbamoyl sulfides **1** into radical cation **5** by radical-chain propagation cannot be excluded at the current stage.[8,20] Indeed, when we irradiated **1a** in the presence of **2a** with blue LEDs for 1 h, the corresponding **4a** was isolated in 26% yield, while an increase in yield (41%) was obtained when **1a** was stirred under dark conditions for 23 h after 1 h irradiation (see the Supporting Information). According to these experiments, both mechanisms may proceed simultaneously.

CONCLUSION

In summary, we have developed an efficient photoredox-catalyzed coupling strategy for the construction of *N*-substituted azoles from readily available α-amido sulfides. This protocol features mild conditions, a relatively broad scope, and high atom-economy in generating an array of 2-(aminomethyl)azoles with high efficiency. Further investiga-

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230–7236

tions are underway to probe the mechanism and to extend the scope of the *N*-alkylation.

EXPERIMENTAL SECTION

Materials and General Methods. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on plates precoated with silica gel layers. NMR spectra (^{1}H, ^{13}C) were recorded with 500 and 300 MHz spectrometers. Flash column chromatography was carried out using 40−63 μm particle sized silica gel. Preparative thin-layer chromatography (prep TLC) was performed using silica gel 60 F254 plates. Visualization was accomplished by irradiation with UV light at 254 nm. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer in positive-ion or negative-ion detection mode. Infrared spectra were taken using solids or neat oils on a diamond surface, and the results are given in cm^{-1}. All reactions were carried out under air atmosphere in oven-dried glassware with magnetic stirring. Visible light irradiations were performed with a Flexled INSPIRE LED lamp (3.6 W; λ = 465 nm). Ru(bpy)$_3$(PF$_6$)$_2$ was purchased from Sigma-Aldrich. All other commercially available reagents and solvents were used without further purification. The α-amido sulfides **1** were prepared according to literature procedures.[7b,c]

General Procedure. A flame-dried test tube, flushed with air, was charged with the corresponding α-amido sulfide **1** (0.1 mmol, 1.0 equiv) and dissolved in MeCN (0.5 mL) and *t*-BuOH (0.1 mL, 10 equiv). Ru(bpy)$_3$(PF$_6$)$_2$ **3a** (2.2 mg, 2.50 mol %) and then the corresponding azole **2** (0.15 mmol, 1.50 equiv) were added. The resultant reaction mixture was irradiated with blue LEDs during 24 h. The reaction mixture was then directly purified by flash chromatography on silica gel (*n*-heptane/EtOAc) to afford the corresponding pure compound **4a**−**u**.

*tert-Butyl (3-Phenyl-1-(1H-pyrazol-1-yl)propyl)carbamate (**4a**).*[10] Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3 to afford 26.6 mg of a colorless solid, 88% yield. Mp: 86−97 °C. IR (cm^{-1}): 3249, 2973, 1698, 1529, 1446, 1407, 1366, 1294, 1239, 1148, 1095, 1047, 1010, 990, 958, 863, 804, 761, 698. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.63 (s, 1H), 7.57 (s, 1H), 7.31 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.1 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 6.26 (s, 1H), 5.84 (d, J = 9.2 Hz, 1H), 5.77 (m, 1H), 2.54−2.51 (m, 3H), 2.43−2.36 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 154.7, 140.3, 140.2, 130.0, 128.6 (×2), 128.5 (×2), 126.3, 104.9, 80.3, 66.4, 36.0, 31.5, 28.3 (×3). HRMS (ESI TOF): m/z = 324.1702 [M + Na]$^+$, $C_{17}H_{23}N_3O_2Na$ requires 324.1688.

*tert-Butyl (1-(1H-Pyrazol-1-yl)heptyl)carbamate (**4b**).* Reaction on 32 mg (0.092 mmol) of *tert*-butyl (1-(phenylthio)heptyl)carbamate (**1b**). Eluent for the flash column chromatography: heptane/ethyl acetate 7/3, to afford 24.3 mg of a colorless solid, 87% yield. Mp: 60−61 °C. IR (cm^{-1}): 3213, 2930, 1702, 1537, 1448, 1404, 1390, 1363, 1299, 1280, 1248, 1158, 1088, 1046, 1000, 869, 760, 747, 686. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.48 (s, 2H), 6.13 (s, 1H), 5.72 (br s, 1H), 5.52 (br s, 1H), 2.12 (br s, 1H), 1.98 (br s, 1H), 1.33 (s, 9H), 1.28−1.08 (m, 8H), 0.78 (t, J = 6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 154.8, 140.0, 129.6, 104.7, 80.2, 67.2, 34.7, 31.6, 28.6, 28.3 (×3), 25.3, 22.5, 14.0. HRMS (ESI TOF): m/z = 304.2004 [M + Na]$^+$, $C_{15}H_{27}N_3O_2Na$ requires 304.2001.

*tert-Butyl (1-(1H-Pyrazol-1-yl)propyl)carbamate (**4c**).* Reaction on 21.9 mg (0.099 mmol) of *tert*-butyl (2-methyl-1-(phenylthio)propyl)-carbamate (**1c**). Eluent for flash column chromatography: heptane/ethyl acetate 9/1 to afford 13.8 mg of a colorless solid, 61% yield. Mp: 75−76 °C. IR (cm^{-1}): 3208, 2973, 1714, 1699, 1543, 1366, 1302, 1288, 1247, 1163, 1097, 1042, 1004, 827, 764, 742. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.58 (s, 2H), 6.23 (s, 1H), 5.74−5.66 (m, 2H), 2.23−1.99 (m, 2H), 1.42 (s, 9H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 154.8, 140.0, 129.7, 104.7, 80.2, 68.5, 28.2 (×3), 28.0, 9.8. HRMS (ESI TOF): m/z = 226.1552 [M + H]$^+$, $C_{11}H_{20}N_3O_2$ requires 226.1556.

*tert-Butyl (2-(Benzyloxy)-1-(1H-pyrazol-1-yl)ethyl)carbamate (**4d**).* Reaction on 31.1 mg (0.099 mmol) of *tert*-butyl (2-(benzyloxy)-1-(ethylthio)ethyl)carbamate (**1d**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3 to afford 18.5 mg of a colorless solid, 58% yield. Mp: 83−84 °C. IR (cm^{-1}): 3219, 2969, 2931, 2891, 1698, 1525, 1369, 1308, 1241, 1155, 1134, 1087, 1042, 1027, 957, 757, 737, 699. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.64 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.39−7.28 (m, 3H), 7.26−7.24 (m, 2H), 6.29 (t, J = 2.0 Hz, 1H), 6.02 (m, 1H), 5.86 (d br, J = 8.5 Hz, 1H), 4.48 (s, 2H), 4.00−3.89 (m, 2H), 1.45 (s, 9H) . ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 154.6, 140.0, 137.4, 129.2, 128.5 (×2), 127.9, 127.7 (×2), 105.2, 80.6, 73.4, 70.5, 66.3, 28.2 (×3). HRMS (ESI TOF): m/z = 318.1804 [M + H]$^+$, $C_{17}H_{24}N_3O_3$ requires 318.1818

*tert-Butyl (2-(Benzyloxy)-1-(1H-pyrazol-1-yl)ethyl)carbamate (**4e**).* Reaction on 29.1 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylprop-2-yn-1-yl)carbamate (**1e**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3 to afford 14 mg of white foam, 47% yield. IR (cm^{-1}): 3241, 2978, 2240, 1705, 1512, 1492, 1444, 1394, 1368, 1324, 1247, 1155, 1085, 1046, 1027, 1009, 994, 966, 918, 862, 804, 756, 691. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.70 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.47−7.42 (m, 2H), 7.34−7.27 (m, 3H), 6.85 (d, J = 9.2 Hz, 1H), 6.27 (t, J = 1.8 Hz, 1H), 5.94 (d, J = 9.2 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 140.9, 132.2 (×2), 129.4, 128.7, 128.5 (×2), 121.3, 106.1 (×2), 86.0, 82.6, 59.2, 29.9, 28.2 (×3). HRMS (ESI TOF): m/z = 320.1381 [M + Na]$^+$, $C_{17}H_{19}N_3O_2Na$ requires 320.1375. m/z = 126.1552 [M + H]$^+$, $C_{12}H_{20}N_3O_2$ requires 126.1556

*tert-Butyl (2-Methyl-1-(1H-pyrazol-1-yl)propyl)carbamate (**4f**).* Reaction on 22.1 mg (0.099 mmol) of *tert*-butyl (2-methyl-1-(phenylthio)propyl)carbamate (**1f**). Eluent for flash column chromatography: heptane/ethyl acetate 7/3 to afford 13.7 mg of a colorless solid, 57% yield. Mp: 116−117 °C. IR (cm^{-1}): 3223, 2974, 1703, 1537, 1392, 1366, 1300, 1248, 1157, 1088, 1041, 1017, 939, 876, 853, 810, 754, 701. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.55 (s, 1H), 7.51 (s, 1H), 6.21 (s, 1H), 5.52 (d, J = 7.7 Hz, 1H), 5.37 (t, J = 9.0 Hz, 1H), 2.38 (h, J = 6.5 Hz, 1H), 1.40 (s, 9H), 1.06 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 155.2, 140.0, 130.0, 104.4, 80.1, 72.8, 33.1, 28.2 (×3), 18.8, 18.6. HRMS (ESI TOF): m/z = 240.1715 [M + H]$^+$, $C_{12}H_{22}N_3O_2$ requires 240.1712 and m/z = 262.1534 [M + Na]$^+$, $C_{12}H_{21}N_3O_2Na$ requires 262.1531

*tert-Butyl (Cyclopropyl(1H-pyrazol-1-yl)methyl)carbamate (**4g**).* Reaction on 21.3 mg (0.099 mmol) of *tert*-butyl (cyclopropyl-(ethylthio)methyl)carbamate (**1g**). Eluent for flash column chromatography: heptane/ethyl acetate 9/1 to afford 9.8 mg of a colorless solid, 41% yield. Mp: 85−86 °C. IR (cm^{-1}): 3343, 3006, 2932, 1690, 1528, 1309, 1251, 1235, 1152, 1021, 758. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.59 (s, 1H), 7.56 (s, 1H), 6.25 (t, J = 2.0 Hz, 3H), 5.75 (m, 1H), 5.20 (t, J = 8.5 Hz, 1H), 1.64 (m, 1H), 1.43 (s, 9H), 0.75−0.35 (m, 2H) . ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 154.9, 139.8, 128.8, 104.9, 80.4, 71.0, 28.3 (×3), 15.9, 3.5 (×2). HRMS (ESI TOF): m/z = 260.1373 [M + Na]$^+$, $C_{12}H_{19}N_3O_2Na$ requires 260.1375.

*tert-Butyl (Phenyl(1H-pyrazol-1-yl)methyl)carbamate (**4h**).* Reaction on 26.7 mg (0.099 mmol) of *tert*-butyl ((ethylthio) (phenyl)-methyl)carbamate (**1h**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3 to afford 16.3 mg of a colorless solid, 60% yield. Mp: 125−126 °C. IR (cm^{-1}): 3251, 2968, 1702, 1530, 1390, 1365, 1329, 1269, 1242, 1176, 1154, 1046, 1009, 918, 868, 817, 765. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.67 (s br, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.40−7.33 (m, 3H), 7.20−7.18 (m, 2H), 7.15 (d br, J = 8.7 Hz, 1H), 6.33 (t, J = 2.0 Hz, 1H), 6.03 (d br, J = 8.6 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 154.6, 140.4, 138.2, 129.4, 128.8 (×2), 128.7, 126.2 (×2), 105.4, 80.8, 69.2, 28.3 (×3). HRMS (ESI TOF): m/z = 296.1362 [M + Na]$^+$, $C_{15}H_{19}N_3O_2Na$ requires 296.1375.

*tert-Butyl ((2-Bromophenyl)(1H-pyrazol-1-yl)methyl)carbamate (**4i**).* Reaction on 34.6 mg (0.100 mmol) of *tert*-butyl ((2-bromophenyl) (ethylthio)methyl)carbamate (**1i**). Eluent for the preparative TLC: heptane/ethyl acetate 2/8 to afford 23.2 mg of a white foam, 66% yield. IR (cm^{-1}): 2926, 1702, 1509, 1367, 1248, 1153, 1027, 754. ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.73−7.66 (m, 1H), 7.64−7.55 (m, 1H), 7.36−7.26 (m, 2H), 7.24−7.15 (m, 2H),

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230−7236

6.34−6.26 (m, 1H), 5.91−5.64 (m, 1H), 3.85 (s, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 140.6, 137.4, 133.5, 130.4, 128.1, 128.0, 125.0, 112.4, 111.8, 105.7, 102.4, 56.0, 28.3 (×3). HRMS (ESI TOF): m/z = 374.0470 $[M + Na]^+$, $C_{15}H_{18}BrN_3O_2Na$ requires 374.0480.

*Benzyl (3-Phenyl-1-(1H-pyrazol-1-yl)propyl)carbamate (**4j**).* Reaction on 33 mg (0.100 mmol) of benzyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1j**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3 to afford 28.6 mg of a colorless oil, 85% yield. IR (cm^{-1}): 3302, 3029, 1703, 1529, 1497, 1231, 1043, 1029, 748, 696. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.65 (s, 1H), 7.60 (s, 1H), 7.40−7.20 (m, 8H), 7.14−7.11 (m, 2H), 6.41 (d br, J = 9.2 Hz, 1H), 6.28 (s, 1H), 5.81 (t, J = 8.1 Hz, 1H), 5.16 (d, J = 12.1 Hz, 1H), 5.00 (d, J = 12.3 Hz, 1H), 2.63−2.32 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.5, 140.4, 140.1, 136.0, 130.1, 128.6 (×2), 128.5 (×2), 128.4 (×2), 128.2, 128.1, 126.3, 126.1, 105.0, 67.1, 66.8, 35.8, 31.4. HRMS (ESI TOF): m/z = 336.1703 $[M + H]^+$, $C_{20}H_{22}N_3O_2$ requires 336.1712.

*tert-Butyl (1-(4-Nitro-1H-pyrazol-1-yl)-3-phenylpropyl)carbamate (**4k**).* Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 6/4 to afford 22.9 mg of a colorless solid, 66% yield. Mp: 140−141 °C. IR (cm^{-1}): 3333, 3142, 2980, 1689, 1524, 1512, 1315, 1289, 1274, 1154, 861, 817, 752, 705. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.29 (s br, 1H), 8.15 (s, 1H), 7.36−7.23 (m, 3H), 7.16−7.13 (m, 2H), 5.73−5.57 (m, 2H), 2.67−2.32 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.3, 139.3, 136.4, 135.3, 128.8 (×2), 128.3 (×2), 126.7 (×2), 81.4, 68.2, 35.1, 31.3, 28.2 (×3). HRMS (ESI TOF): m/z = 381.1337 $[M + Cl]^-$, $C_{17}H_{22}N_4O_4Cl$ requires 381.1330.

*tert-Butyl (1-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-phenylpropyl)carbamate (**4l**).* Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 6/4 to afford 26.1 mg of a colorless solid, 79% yield. Mp: 121−122 °C. IR (cm^{-1}): 3187, 2981, 1703, 1538, 1454, 1273, 1243, 1156, 1054, 1031, 779, 767, 717, 694. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32−7.13 (m, 5H), 6.10 (d br, J = 9.2 Hz, 1H), 5.77 (s, 1H), 5.70 (m, 1H), 2.52−2.33 (m, 4H), 2.27 (s, 3H), 2.24 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 148.4, 140.7, 139.6, 128.5 (×2), 128.4 (×2), 126.1, 104.7, 79.0, 62.2, 36.4, 31.5, 28.3 (×3), 13.7, 10.7. HRMS (ESI TOF): m/z = 330.2169 $[M + H]^+$, $C_{19}H_{28}N_3O_2$ requires 330.2182.

*tert-Butyl (1-(3,5-Dimethyl-1H-pyrazol-1-yl)octyl)carbamate (**4m**).* Reaction on 28.9 mg (0.099 mmol) of *tert*-butyl (1-(phenylthio)octyl)carbamate (**1k**). Eluent for flash column chromatography: heptane/ethyl acetate 7/3 to afford 29 mg of oil, 59% yield. IR (cm^{-1}): 3190, 2927, 2857, 1705, 1556, 1459, 1365, 1350, 1290, 1273, 1246, 1178, 1048, 1001, 873, 780, 753. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.74 (s, 1H), 5.71−5.59 (m, 2H), 2.35 (s, 3H), 2.23 (s, 3H), 2.16−1.88 (m, 2H), 1.41 (s, 9H), 1.34−0.99 (m, 10H), 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 148.2, 134.4, 104.4, 79.8, 62.8, 35.3, 31.6, 29.0, 28.7, 28.2 (×3), 25.2, 22.5, 13.9, 13.6, 10.7. HRMS (ESI TOF): m/z = 324.2646 $[M + H]^+$, $C_{18}H_{34}N_3O_2$ requires 324.2651.

*tert-Butyl (1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-methylpropyl)carbamate (**4n**).* Reaction on 22.1 mg (0.099 mmol) of *tert*-butyl (2-methyl-1-(phenylthio)propyl)carbamate (**1f**). Eluent for flash column chromatography: heptane/ethyl acetate 7/3 to afford 20.1 mg of a white foam, 75% yield. IR (cm^{-1}): 3196, 2977, 1699, 1539, 1475, 1459, 1390, 1362, 1294, 1247, 1166, 1041, 1010, 950, 881, 858, 845, 779, 738. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.73 (s, 1H), 5.70 (s, 1H), 5.27 (t, J = 9.9 Hz, 1H), 2.42−2.26 (m, 4H), 2.22 (s, 3H), 1.40 (s, 9H), 1.08 (d, J = 6.6 Hz, 3H), 0.64 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.3, 148.3, 139.8, 104.4, 79.9, 68.6, 33.9, 28.4 (×3), 19.2, 18.7, 13.8, 11.0. HRMS (ESI TOF): m/z = 268.2031 $[M + H]^+$, $C_{14}H_{26}N_3O_2$ requires 268.2025.

*tert-Butyl (1-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-phenylpropyl)carbamate (**4o**).* Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 6/4 to afford 27.2 mg of a white foam, 86% yield. IR (cm^{-1}): 3214, 3028, 2977, 2931, 1709, 1521, 1497, 1454, 1391, 1366, 1327, 1292, 1272, 1245, 1162, 1048, 1028, 998, 911, 868, 752, 699. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.47−7.40 (m, 1H), 7.28−7.24 (m, 2H), 7.20−7.15 (m, 1H), 7.12−7.09 (m, 2H), 5.98−5.96 (m, 1H), 5.82−5.75 (m, 1H), 5.63−5.56 (m, 1H), 2.56−2.40 (m, 3H), 2.29 (s, 3H), 2.25 (m, 1H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.5, 139.5, 130.9, 128.6 (×2), 128.5, 126.3, 104.9, 104.5, 66.3, 62.5, 36.1, 31.6, 28.4 (×3), 13.9, 10.8. HRMS (ESI TOF): m/z = 316.2018 $[M + H]^+$, $C_{18}H_{26}N_3O_2$ requires 316.2025.

*tert-Butyl (1-(1H-Imidazol-1-yl)-3-phenylpropyl)carbamate (**4p**).* Reaction on 50 mg (0.10 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3 to afford 32 mg of a colorless solid, 91% yield. Mp: 129−130 °C. IR (cm^{-1}): 3194, 3027, 2972, 1710, 1544, 1366, 1287, 1263, 1250, 1156, 1121, 1045, 1028, 1010, 911, 853, 790, 761, 734, 702, 657. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (s br, 1H), 7.79 (dd, J = 8.8 and 0.9 Hz, 1H), 7.72 (dt, J = 8.4 and 1.0 Hz, 1H), 7.38−7.20 (m, 4H), 7.16−7.11 (m, 3H), 6.49 (d br, J = 9.0 Hz, 1H), 6.07 (m, 1H), 2.72−2.48 (m, 4H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 143.6, 141.3, 139.5, 132.5, 128.7 (×2), 128.4 (×2), 126.6, 123.2, 122.6, 120.3, 110.8, 80.8, 62.4, 36.0, 31.7, 28.2 (×3). HRMS (ESI TOF): m/z = 352.2014 $[M + H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

*tert-Butyl (1-(1H-Imidazol-1-yl)-3-phenylpropyl)carbamate (**4q**).* Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: pure ethyl acetate to afford 6.3 mg of a colorless solid, 21% yield. Mp: 158−159 °C. IR (cm^{-1}): 3181, 2972, 2936, 1702, 1284, 1254, 1218, 1159, 1073, 1047, 1025, 768, 755, 739, 701, 660. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.63 (s br, 1H), 7.26 7.12 (m, 3H), 7.06 6.96 (m, 4H), 5.68 (br s, 1H), 5.35 (br s, 1H), 2.56 (t, J = 7.6 Hz, 2H), 2.24 (m, 2H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.4, 139.5, 135.9, 129.2, 128.7 (×2), 128.4 (×2), 126.6, 116.3, 81.0, 63.2, 36.5, 31.6, 28.3 (×3). HRMS (ESI TOF): m/z = 302.1860 $[M + H]^+$, $C_{17}H_{24}N_3O_2$ requires 302.1869.

*tert-Butyl (1-(1H-Benzo[d]imidazol-1-yl)-3-phenylpropyl)carbamate (**4r**).*[10] Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 2/8 to afford 27.6 mg of a colorless oil, 79% yield. IR (cm^{-1}): 2978, 1706, 1492, 1455, 1366, 1250, 1156, 1047, 1026, 741, 698. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.01 (s br, 1H), 7.80 (s, 1H), 7.51 (br s, 1H), 7.28−7.19 (m, 5H), 7.11−7.09 (m, 2H), 5.99 (br s, 1H), 5.81 (br s, 1H), 2.65 (m, 2H), 2.49 (m, 2H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 143.6, 141.3, 139.5, 132.5, 128.7 (×2), 128.4 (×2), 126.6, 123.2, 122.6, 120.3, 110.8, 80.8, 62.4, 36.0, 31.7, 28.2 (×3). HRMS (ESI TOF): m/z = 352.2010 $[M + H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

*tert-Butyl (1-(1H-Benzo[d]imidazol-1-yl)-2-methylpropyl)carbamate (**4s**).* Reaction on 22.1 mg (0.100 mmol) of *tert*-butyl (2-methyl-1-(phenylthio)propyl)carbamate (**1f**). Eluent for flash column chromatography: heptane/ethyl acetate 2/8 to afford 19.5 mg of a white foam, 67% yield. IR (cm^{-1}): 2976, 1707, 1491, 1457, 1392, 1367, 1310, 1282, 1219, 1158, 1043, 1011, 848, 772, 742. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09−8.00 (m, 1H), 7.86−7.78 (m, 1H), 7.59−7.47 (m, 1H), 7.35−7.24 (m, 2H), 5.86−5.31 (m, 2H), 2.60−2.34 (m, 1H), 1.38 (s, 9H), 1.16 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 143.9, 141.6, 132.8, 123.1, 122.4, 120.4, 110.7 (×2), 68.8, 32.6, 28.2 (×3), 19.0, 18.9. HRMS (ESI TOF): m/z = 290.1865 $[M + H]^+$, $C_{16}H_{24}N_3O_2$ requires 290.1869.

*tert-Butyl (1-(1H-Benzo[d]imidazol-1-yl)-2-(benzyloxy)ethyl)carbamate (**4t**).* Reaction on 31.1 mg (0.100 mmol) of *tert*-butyl (2-(benzyloxy)-1-(ethylthio)ethyl)carbamate (**1d**). Eluent for the preparative TLC: heptane/ethyl acetate 2/8 to afford 27.3 mg of a colorless solid, 74% yield. Mp: 83−84 °C. IR (cm^{-1}): 3219, 2969, 2931, 2891, 1698, 1525, 1369, 1308, 1241, 1155, 1134, 1087, 1042, 1027, 957, 757, 737, 699. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.24 (br s, 1H), 7.81−7.77 (m, 1H), 7.59 (br s, 1H), 7.30−7.17 (m, 7H), 6.20−6.05 (m, 1H), 5.87(d,

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230−7236

J = 8.7 Hz, 1H), 4.47 (s, 2H), 3.92−3.75 (m, 2H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.5, 143.4, 141.7, 136.7, 133.0, 128.8 (×2), 128.4 (×2), 128.1 (×2), 123.3, 122.6, 120.3, 110.6, 74.0, 70.6, 61.2, 28.3 (×3). HRMS (ESI TOF): m/z = 368.1964 $[M + H]^+$, $C_{21}H_{26}N_3O_3$ requires 368.1974.

tert-Butyl (3-Phenyl-1-(9H-purin-9-yl)propyl)carbamate (4u). Reaction on 29.5 mg (0.100 mmol) of *tert*-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 6/4 to afford 28.6 mg of a white foam, 81% yield. IR (cm^{-1}): 2977, 1711, 1595, 1494, 1455, 1392, 1368, 1343, 1299, 1250, 1158, 1049, 909, 850, 794, 736, 700. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.15 (s, 1H), 8.97 (s, 1H), 8.11 (s, 1H), 7.33−7.27 (m, 1H), 7.26−7.16 (m, 2H), 7.14−7.05 (m, 2H), 6.05−5.88 (m, 2H), 2.86−2.53 (m, 4H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 152.3, 150.9, 148.8, 145.3, 139.3, 128.7 (×2), 128.3 (×2), 126.6, 63.8, 60.5, 34.6, 31.7, 28.2 (×3), 26.2, 21.2. HRMS (ESI TOF): m/z = 354.1928 $[M + H]^+$, $C_{19}H_{24}N_5O_2$ requires 354.1930.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01108.

Experimental details, characterization of new compounds, and selected NMR and HPLC spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: geraldine.masson@cnrs.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

L.J. thanks the Université Paris-Sud for doctoral fellowships, and G.L. thanks Labex Charm3at for financial support of Master studies.

■ REFERENCES

(1) For recent selected examples, see: (a) Liu, J.-J.; Sun, J.; Fang, Y.-B.; Yang, Y.-A.; Jiao, R.-H.; Zhu, H.-L. *Org. Biomol. Chem.* **2014**, *12*, 998. (b) Abdel-Magid, A. F. *ACS Med. Chem. Lett.* **2014**, *5*, 730. (c) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. *Eur. J. Med. Chem.* **2013**, *69*, 735. (d) Chang, C.-P.; Wu, C.-H.; Song, J.-S.; Chou, M.-C.; Wong, Y.-C.; Lin, Y.; Yeh, T.-K.; Sadani, A. A.; Ou, M.-H.; Chen, K.-H.; Chen, P.- H.; Kuo, P.-C.; Tseng, C.-T.; Chang, K.-H.; Tseng, S.-L.; Chao, Y.-S.; Hung, M.-S.; Shia, K.-S. *J. Med. Chem.* **2013**, *56*, 9920. (e) Ouyang, G.; Cai, X.-J.; Chen, Z.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y.; Zeng, S. *J. Agric. Food Chem.* **2008**, *56*, 10160. (f) Sridhar, R.; Perumal, P. T.; Etti, S.; Shanmugam, G.; Ponnuswamy, M. N.; Prabavathy, V. R.; Mathivanan, N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6035.

(2) For recent selected examples, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (b) de Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1. (c) Koch, P.; Bauerlein, C.; Jank, H.; Laufer, S. *J. Med. Chem.* **2008**, *51*, 5630. (d) Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 378. (e) Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 378. (f) Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y.-H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697. (g) Cui, B.; Zheng, B. L.; He, K.; Zheng, Q. Y. *J. Nat. Prod.* **2003**, *66*, 1101.

(3) For reviews on pyrazole synthesis, see: (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Dadiboyena, S.; Nefzi, A. *Eur. J. Med. Chem.* **2011**, *46*, 5258. (c) Yet, L. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4, p 1. (d) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.

(4) For selected examples of pyrazole synthesis, see: (a) Kamal, A.; Sastry, K. N. V.; Chandrasekhar, D.; Mani, G. S.; Adiyala, P. R.; Nanubolu, J. B.; Singarapu, K. K.; Maurya, R. A. *J. Org. Chem.* **2015**, *80*, 4325. (b) Zhang, X.; Kang, J.; Niu, P.; Wu, J.; Yu, W.; Chang, J. *J. Org. Chem.* **2014**, *79*, 10170. (c) Harigae, R.; Moriyama, K.; Togo, H. *J. Org. Chem.* **2014**, *79*, 2049. (d) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6255. (e) Wang, Q.; Zhang, Z.; Du, Z.; Hua, H.; Chen, S. *Green Chem.* **2013**, *15*, 1048. (f) Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3636. (g) Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 1317. (h) Hu, J.; Chen, S.; Sun, Y.; Yang, J.; Rao, Y. *Org. Lett.* **2012**, *14*, 5030.

(5) For reviews on imidazole synthesis, see: (a) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4, p 143. (b) Kamijo, S.; Yamamoto, Y. *Chem. - Asian J.* **2007**, *2*, 568. (c) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, *2006*, 965. (d) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571.

(6) Selected recent examples synthesis of imidazoles, see (a) Padala, A. K.; Kumar, R. R.; Athimoolam, S.; Ahmed, Q. N. *Org. Lett.* **2016**, *18*, 96. (b) Xu, L.; Li, H.; Liao, Z.; Lou, K.; Xie, H.; Li, H.; Wang, W. *Org. Lett.* **2015**, *17*, 3434. (c) Liu, X.; Wang, D.; Chen, Y.; Tang, D.; Chen, B. *Adv. Synth. Catal.* **2013**, *355*, 2798. (d) Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473. (e) Lavallo, V.; Grubbs, R. H. *Science* **2009**, *326*, 559. (f) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050. (g) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10662.

(7) (a) Matthies, D. *Synthesis* **1972**, *1972*, 380. (b) Zhang, H.; Lian, C.-X.; Yuan, W.-C.; Zhang, X.-M. *Synlett* **2012**, *23*, 1339. (c) Xuan, J.; Feng, Z.-J.; Duan, S.-W.; Xiao, W.-J. *RSC Adv.* **2012**, *2*, 4065. (d) Mao, X.; Wu, Y.; Jiang, X.; Liu, X.; Cheng, Y.; Zhu, C. *RSC Adv.* **2012**, *2*, 6733. (e) Liu, X. W.; Zhang, Y. M.; Wang, L.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *J. Org. Chem.* **2008**, *73*, 6207. (f) Zhang, Y. M.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Org. Lett.* **2007**, *9*, 3813.

(8) For recent reviews on photoredox catalysis, see: (a) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00018. (b) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.5b00662. (c) Cao, M.-Y.; Ren, X.; Lu, Z. *Tetrahedron Lett.* **2015**, *56*, 3732. (d) Kärkäs, M. D.; Matsuura, B. S.; Stephenson, C. R. J. *Science* **2015**, *349*, 1285. (e) Meggers, E. *Chem. Commun.* **2015**, *51*, 3290. (f) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (g) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(9) For reviews, see: (a) Kataja, A. O.; Masson, G. *Tetrahedron* **2014**, *70*, 8783. For selected examples of α-aminosulfides as *N*-alkyliminium precursors, see: (b) George, N.; Bekkaye, M.; Alix, A.; Zhu, J.; Masson, G. *Chem. - Eur. J.* **2014**, *20*, 3621. (c) George, N.; Bekkaye, M.; Masson, G.; Zhu, J. *Eur. J. Org. Chem.* **2011**, *2011*, 3695. (d) Agami, C.; Couty, F.; Poursoulis, M.; Vaissermann, J. *Tetrahedron* **1992**, *48*, 431. (e) Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47*, 4343.

(10) Lebée, C.; Languet, M.; Allain, C.; Masson, G. *Org. Lett.* **2016**, *18*, 1478.

(11) Wever, W. J.; Cinelli, M. A.; Bowers, A. A. *Org. Lett.* **2013**, *15*, 30.

(12) Previous work in our group in the area of visible light photocatalysis: (a) Courant, T.; Masson, G. *Chem. - Eur. J.* **2012**, *18*, 423. (b) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240. (c) Dagousset, G.; Carboni, A.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 4340. (d) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Chem. Commun.* **2014**, *50*, 14197. (e) Carboni, C.; Dagousset, G.; Magnier, E.; Masson, G. *Synthesis* **2015**, *47*, 2439. For previous work in our group in the area of single-electron oxidative process, see (f) Bekkaye, M.; Masson, G. *Org. Lett.* **2014**, *16*, 1510.

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230−7236

(13) (a) SmithKline. U.S. Patent 3994954, 1976. (b) Nuss, J. M.; Harrison, S. D.; Ring, D. B.; Boyce, R. S.; Johnson, K.; Pfister, K. B.; Ramurthy, S.; Seely, L.; Wagman, A. S.; Desai, M.; Levine, B. H. U.S. Patent 2002/156087A1, 2002. (c) May, J. A.; Zinke, P. W. U.S. Patent 6884816, 2005. May, J. A.; Zinke, P. W. U.S. Patent 6933392, 2005. (d) Bayer Cropscience GMBH WO 200650803A1, 2006. (e) Hu, S.; Li, H.; Long, W.; Shen, X.; Tan, F.; Wang, Y. WO 20126958A1, 2012.
(14) For recent reviews on organic photoredox catalysis, see: (a) Hari, D. P.; König, B. *Chem. Commun.* **2014**, *50*, 6688. (b) Fukuzumi, S.; Ohkubo, K. *Org. Biomol. Chem.* **2014**, *12*, 6059. (c) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355.
(15) The effect of the protic solvent may increase the solubility of radical cation **2** as described in previous reports; see: (a) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274. (b) Wever, W. J.; Cinelli, M. A.; Bowers, A. A. *Org. Lett.* **2013**, *15*, 30. See also ref 9. We also observed that the presence *t*-BuOH reduces the oxidation potential of **1**; see ref 8.
(16) Kano, T.; Yurino, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 11509 and references cited therein.
(17) For a recent review, see: (a) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977. (b) Beatty, J. B.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474.
(18) For selected articles on mechanistic aspects of the photochemical reaction in presence of molecular oxygen, see: (a) Tucker, J. W.; Narayanam, J. M. R.; Shah, P. S.; Stephenson, C. R. J. *Chem. Commun.* **2011**, *47*, 5040. (b) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (c) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171. (d) Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615. (e) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013**, *135*, 1823. (f) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 13286. (g) Dai, X.; Cheng, D.; Guan, B.; Mao, B.; Xu, X.; Li, X. *J. Org. Chem.* **2014**, *79*, 7212. (h) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326.
(19) Hydroperoxyl radical can spontaneously disproportionate to hydrogen peroxide (H_2O_2) and singlet dioxygen. In order to prove the formation of H_2O_2 during the process, we tried to capture it by olefins such as styrene or cyclohexene. Unfortunately, in both cases, no epoxide resulting from the trapping of the H_2O_2 could be observed.
(20) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426.

DOI: 10.1021/acs.joc.6b01108
J. Org. Chem. 2016, 81, 7230−7236