JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

Tetrasubstituted 2-Imidazolones via Ag(I)-Catalyzed Cycloisomerization of Propargylic Ureas

Vsevolod A. Peshkov,[†] Olga P. Pereshivko,[†] Sweta Sharma,[†,‡] Thirumal Meganathan,[‡] Virinder S. Parmar,[‡] Denis S. Ermolat'ev,*[,†] and Erik V. Van der Eycken*[,†]

[†]Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

[‡]Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi-110 007, India

Supporting Information

ABSTRACT: A one-pot protocol based on a Ag(I)-catalyzed cycloisomerization of propargylic ureas, derived from secondary propargylamines and isocyanates, was developed for the generation of the 2-imidazolone core.

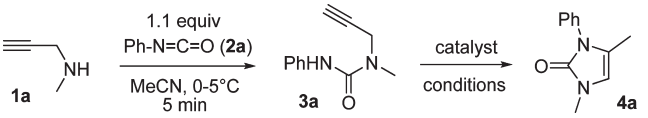
The role of silver catalysis rapidly grows, providing novel methodologies for C−C and C−X (X = O, N) bond formation to address a wide range of synthetic targets.[1] Ag(I) salts are found to be efficient promoters for decarboxylative transformations,[2] modulators of the decomposition of diazo compounds,[3] and C−H activators of terminal alkynes.[4] Of particular interest are the Ag(I)-catalyzed heterocyclizations involving the activation of the triple bond.[5,6] These transformations allow to obtain a diverse set of O- and N-heterocycles starting from readily available precursors.

We have recently described a rapid and diversity-oriented Ag(I)-mediated synthesis of 2-iminoimidazolines via guanylation of secondary propargylamines followed by 5-*exo-dig* cyclization.[7] 2-Iminoimidazolines possess a strong structural resemblance with 2-imidazolones, which are widespread among pharmaceutically interesting compounds such as human dopamine D_4 receptor antagonists,[8] MurB enzyme inhibitors,[9] potential antitumor agents,[10] and antioxidants.[11]

Herein we wish to disclose the synthesis of 2-imidazolones from secondary propargylamines and isocyanates via a one-pot acylation, Ag(I)-catalyzed cycloisomerization procedure. To the best of our knowledge, there is only one reported example regarding the transition-metal-catalyzed ring closure of propargylic urea.[12] In this process the 2-imidazolone core results from a primary propargylamine and a tosyl isocyanate via sequential acylation and Au(I)-catalyzed 5-*exo-dig* cyclization followed by *p*TsOH-promoted double-bond migration.

We have started our study with the investigation of the condensation between methylpropargylamine (**1a**) and phenyl isocyanate (**2a**) in acetonitrile at 0−5 °C. This reaction appeared to be very fast, delivering the propargylic urea **3a** in a mere 5 min. However, running the reaction for an additional 2 h at room temperature did not provide the cycloisomerization product **4a**, but the propargylic urea **3a** was obtained in 81% yield (Table 1, entry 1). Also addition of Ag(I) catalyst at room temperature did not result in the formation of 2-imidazolone **4a**, and the corresponding urea **3a** was again isolated as the sole reaction product (Table 1, entry 2). Gratifyingly, the desired 2-imidazolone **4a** was formed in high yields when the temperature was increased to 80 °C employing 10 mol % of various Ag(I) catalysts (Table 1, entries 3−6). The best result was obtained with AgOTf (Table 1, entry 3). Performing the reaction with 10 mol % of $Cu(OTf)_2$ at 80 °C for the 2 h, the desired 2-imidazolone **4a** was isolated in a very low yield of 8% next to the 85% of the uncyclized urea **3a** (Table 1, entry 7). This is remarkable as

Table 1. Optimization of the One-Pot Formation of 2-Imidazolone 4a Starting from Methylpropargylamine (1a)

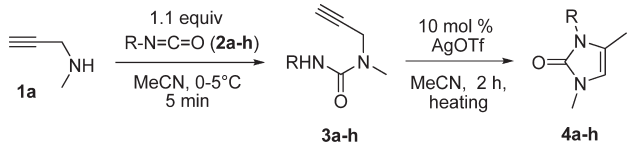


entry	catalyst	conditions	yield[a]
1		MeCN, rt, 2 h	− (81)[b]
2	10 mol % AgOTf	MeCN, rt, 2 h	− (82)[b]
3	10 mol % AgOTf	MeCN, 80 °C, 2 h	94
4	10 mol % $AgOOCCF_3$	MeCN, 80 °C, 2 h	86
5	10 mol % $AgSbF_6$	MeCN, 80 °C, 2 h	89
6	10 mol % $AgNO_3$	MeCN, 80 °C, 2 h	76
7	10 mol % $Cu(OTf)_2$	MeCN, 80 °C, 2 h	8 (85)[b]

[a] Isolated yields are reported. [b] Isolated yield for the propargylic urea **3a** is given in parentheses.

Received: April 18, 2011
Published: June 03, 2011

Table 2. Isocyanate Substrate Scope for the One-Pot Formation of 2-Imidazolones 4



entry	R (isocyanate)	temp (°C)	product	yield[a]
1	Ph (**2a**)	80	**4a**	94
2	*p*-Tol (**2b**)	80	**4b**	93
3	PMP (**2c**)	80	**4c**	91
4	*p*-FC_6H_4 (**2d**)	80	**4d**	82
5	*m*-ClC_6H_4 (**2e**)	110	**4e**	91
6	Hex (**2f**)	80	**4f**	34
7	Hex (**2f**)	110	**4f**	29
8	Bn (**2g**)	80	**4g**	32 (42)[b]
9	Ts (**2h**)	80	**4h**	66

[a] Isolated yields are reported. [b] Isolated yield for the propargylic urea **3g** is given in parentheses.

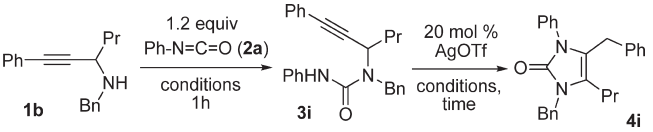
$Cu(OTf)_2$ is known to be an efficient triple bond activator for ring-closure reactions with nitrogen nucleophiles.[13]

Having the optimized conditions at hand (Table 1, entry 3) we evaluated the scope and limitations of our procedure, applying various isocyanates **2** (Table 2). With aromatic isocyanates **2a**−**e** the corresponding 2-imidazolones **4a**−**e** were obtained in high yields ranging from 82% to 94% (Table 2, entries 1−5). For the *m*-chlorophenyl isocyanate (**2e**) a higher temperature of 110 °C was required to reach full conversion of the propagylic urea **3e** into the final 2-imidazolone **4e** (Table 2, entry 5). The use of aliphatic hexyl and benzyl isocyanates **2f,g** resulted in low conversions of intermediate ureas **3f,g** into the corresponding 2-imidazolones **4f, g**, which were obtained in low yields of 34% and 32% respectively (Table 2, entries 6 and 8). An attempt to improve the yield of **4f** by increasing the reaction temperature to 110 °C met with failure (Table 2, entry 7). The reaction of methyl propargylamine (**1a**) with tosyl isocyanate (**2h**) resulted in the formation of the 2-imidazolone **4h** in a moderate yield of 66%.

Then we decided to adapt our protocol for the synthesis of tetrasubstituted 2-imidazolones **4**.[14] We chose the reaction between *N*-benzyl-1-phenylhex-1-yn-3-amine (**1b**) and phenyl isocyanate (**2a**) as a model. The formation of the propargylic urea **3i** in acetonitrile occurred at 80 °C within 1 h. However, after silver triflate addition and 2 h of further heating at the same temperature, only traces of 2-imidazolone **4i** could be observed (Table 3, entry 1). Increasing the reaction temperature to 110 °C resulted in the formation of **4i** in a meager yield of 18% (Table 3, entry 2). When the solvent was switched to DCE, an improved yield of 35% was obtained (Table 3, entry 3). Gratifyingly, reaction in toluene resulted in the isolation of the desired 2-imidazolone **4i** in a good yield of 72% (Table 3, entry 4). A further attempt to improve the conversion of urea **3i** into **4i** by increasing the reaction time to 4 h resulted in a decreased yield of 57% (Table 3, entry 5).

Next we applied this modified protocol for the generation of a small library of tetrasubstituted 2-imidazolones. An array of aromatic isocyanates and variously substituted propargylamines, which are readily available via our recently reported A^3-coupling protocol,[15] was successfully explored (Table 4). Propargylamines

Table 3. Adaption of the Protocol for the Synthesis of Tetrasubstituted 2-Imidazolones



entry	conditions	time (h)	yield[a]
1	MeCN, 80 °C	2	tr, (81)[b]
2	MeCN, 110 °C	2	18
3	DCE, 110 °C	2	35
4	toluene, 110 °C	2	72
5	toluene, 110 °C	4	57

[a] Isolated yields are reported. [b] Isolated yield for the propargylic urea **3i** is given in parentheses.

1b,c,f bearing both an unbranched aliphatic R^2-substituent and an aromatic R^3-substituent, provided good yields of the target 2-imidazolones **4i**−**m,r**−**t** ranging from 50% to 72%. However when propargylamine **1d** was used, a significant drop of the yield was observed. The corresponding 2-imidazolones **4n** and **4o** were obtained in low yields of 33% and 32%, respectively, probably due to the bulkiness of the branched R^2-substituent. When propargylamine **1e** was used, the corresponding 2-imidazolones **4p** and **4q** were also obtained in low yields of 25% and 21%, respectively. This might be ascribed to the lower electrophilicity of the triple bond bearing an aliphatic R^3-substituent.

A plausible mechanism for the one-pot formation of the 2-imidazolones **4** is presented in Scheme 1. Propargylic urea **3**, derived from the corresponding propargylamine and isocyanate, undergoes 5-*exo-dig* cyclization through transition state **A**. Subsequent proton transfer in intermediate **B** provides the 2-imidazolone **4′** bearing an exocyclic double bond. Finally, double-bond migration results in the formation of the 2-imidazolone **4**. We presume that this migration process occurs very fast as the formation of the intermediate 2-imidazolones **4′** could not be observed under the applied reaction conditions.[16] However, when reaction with methyl propargylamine (**1a**) and tosyl isocyanate (**2h**) was performed in wet acetonitrile, both **4′h** and **4h** have been isolated in 52% and 20% yield, respectively (Scheme 1). In order to verify the role of the Ag(I) catalyst in the double-bond migration process, we set up two experiments (Scheme 1). Heating a mixture of **4′h** with 10 mol % of AgOTf in dry acetonitrile for 4 h at 80 °C resulted in full conversion into **4h**. Running the same reaction in the absence of AgOTf resulted in 90% conversion as was determined by ^1H NMR. This indicates that the Ag(I) catalyst might participate in the double-bond migration process.

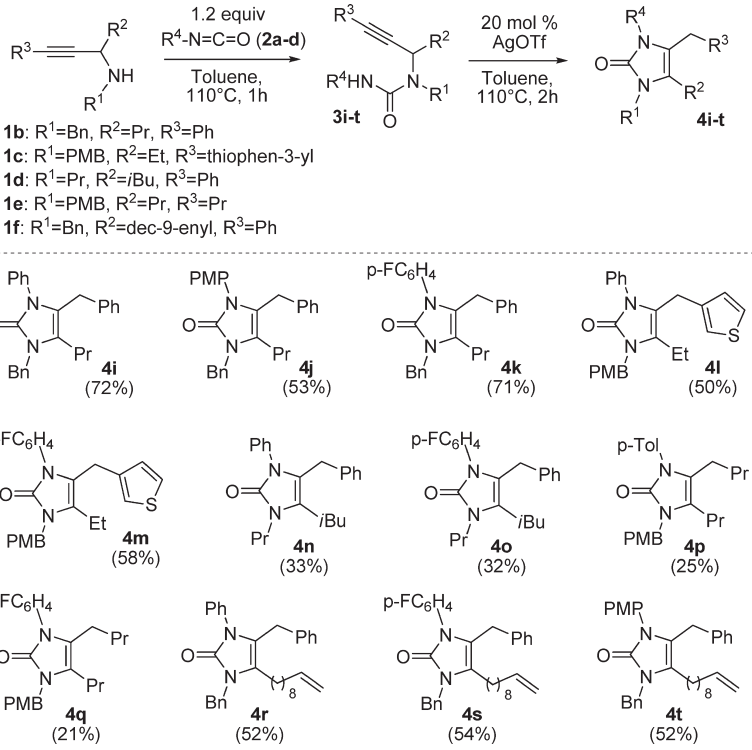
In summary, we have elaborated an efficient one-pot protocol for the construction of the 2-imidazolone core starting from readily available secondary propargylamines. The key step of the process is a Ag(I)-catalyzed cycloisomerization of an *in situ* formed propargylic urea. The method allows the introduction of four points of diversity in a concise way and can be potentially useful for the synthesis of biologically active 2-imidazolone derivatives.

EXPERIMENTAL SECTION

^1H spectra and ^{13}C NMR were recorded with 300 and 75 MHz respectively unless otherwise noted. The ^1H and ^{13}C chemical shifts are

dx.doi.org/10.1021/jo200789t |*J. Org. Chem.* 2011, 76, 5867–5872

Table 4. Scope and Limitations of the Protocol for the Synthesis of Tetrasubstituted 2-Imidazolones



reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. High-resolution EI-mass spectra were recorded with a resolution of 10 000. The ion source temperature was 150−250 °C, as required. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in 10-mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to ambient temperature with air jet cooling.

Synthesis of Starting Propargylamines 1b−f. Propargylamines **1b,d** were synthesized following known procedure.[15]

General Procedure for the Synthesis of Propargylamines 1c,e. Amine (2.0 mmol), aldehyde (2.0 mmol), acetylene (4.0 mmol), copper bromide (76 mg, 0.4 mmol) and toluene (2.0 mL) were loaded to a glass tube with a screw cap. The mixture was degassed and flushed with argon. The reaction vessel was conventionally heated with stirring for 4 h at 100 °C. The resulting reaction mixture was cooled to ambient temperature and subjected to the column chromatography with (EtOAc-hepthane, 1:4) to afford the product.

N-(4-Methoxybenzyl)-1-(thiophen-3-yl)pent-1-yn-3-amine (***1c***). Yield 30%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.35 (m, 1H), 7.34−7.18 (m, 3H), 7.16−7.03 (m, 1H), 6.86 (d, J = 8.5 Hz, 2H), 4.00 (d, J = 12.7 Hz, 1H), 3.87−3.70 (m, 4H), 3.55−3.40 (m, 1H), 1.85−1.60 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 132.2, 130.1, 129.6, 128.2, 125.2, 122.4, 113.8, 90.5, 79.0, 55.3, 51.4, 51.0, 29.2, 10.6; HRMS (EI) calcd for $C_{17}H_{19}ONS$ 285.1187, found 285.1172.

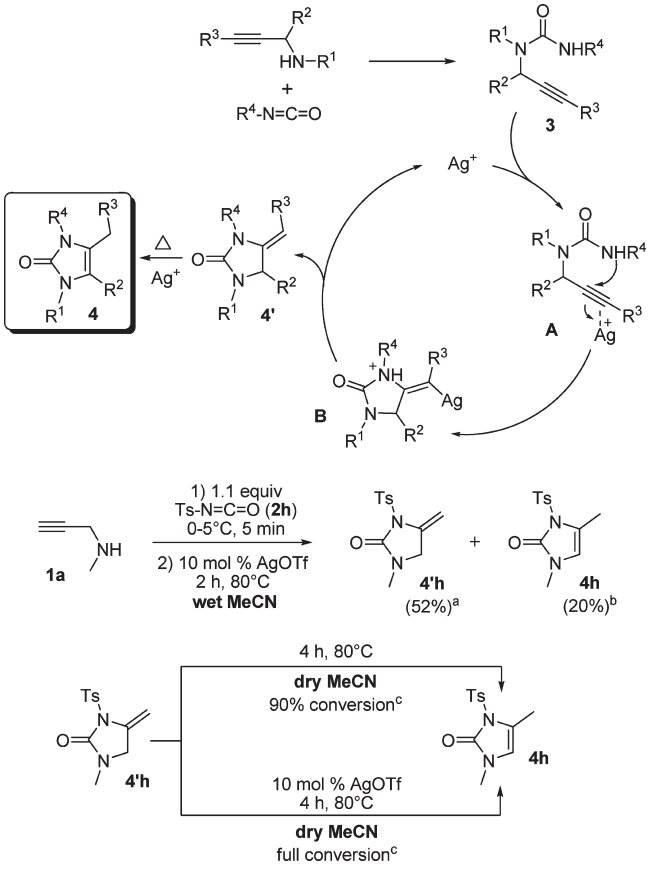
N-(4-Methoxybenzyl)non-5-yn-4-amine (***1e***). Yield 24%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.94 (d, J = 12.6 Hz, 1H), 3.79 (s, 3H), 3.73 (d, J = 12.6 Hz, 1H), 3.40−3.25 (m, 1H), 2.30−2.10 (m, 2H), 1.65−1.40 (m, 6H), 1.01 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 132.5, 129.6, 113.7, 83.7, 81.7, 55.2, 50.8, 49.3, 38.6, 22.5, 20.8, 19.4, 13.9, 13.5; MS (ESI$^+$) calcd for $C_{17}H_{25}ON$ 259.2, found 260.7 $[M + H]^+$.

N-Benzyl-1-phenyltridec-12-en-1-yn-3-amine (***1f***). Benzylamine (214 mg, 2.0 mmol), undec-10-enal (337 mg, 2.0 mmol), phenyl acetylene (409 mg, 4.0 mmol), copper bromide (76 mg, 0.4 mmol), and toluene (2.0 mL) were loaded to a microwave vial equipped with a magnetic stirring bar. The mixture was degassed and flushed with argon. The reaction vessel was sealed and irradiated in the cavity of a CEM-Discover microwave reactor for 25 min at a ceiling temperature of 100 °C and a maximum power of 80 W. The resulting reaction mixture was cooled to ambient temperature and subjected to the column chromatography with (EtOAc/hepthane, 1:4) to afford propargylamine **2d** (364 mg, 51%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.16 (m, 10H), 5.90−5.67 (m, 1H), 5.06−4.82 (m, 2H), 4.08 (d, J = 12.8 Hz, 1H), 3.88 (d, J = 12.8 Hz, 1H), 3.66−3.43 (m, 1H), 2.10−1.93 (m, 2H), 1.80−1.61 (m, 2H), 1.59−1.21 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.2, 139.2, 131.7, 128.4, 128.3, 127.9, 127.0, 123.5, 114.2, 91.2, 84.0, 51.6, 50.1, 36.2, 33.9, 29.6, 29.5, 29.2, 29.0, 26.2; HRMS (EI) calcd for $C_{26}H_{33}N$ 359.2613, found 359.2602.

General Procedure for the Synthesis of the Imidazol-2-ones 4a−h via One-Pot Acylation, Ag(I)-Catalyzed Cycloisomerization. To a solution of methylpropargylamine (**1a**) (69 mg, 1 mmol) in dry MeCN (2.5 mL) was added the appropriate isocyanate **2a−h** (1.1 mmol) at 0−5 °C. The glass tube with reaction mixture was degassed and flushed with argon. After 5 min of stirring, silver triflate (26 mg, 0.1 mmol) was added, and the reaction mixture was sealed and stirred for 2 h at 80 °C. Upon completion of reaction MeCN was removed under reduced pressure. The crude product was loaded onto a

dx.doi.org/10.1021/jo200789t |*J. Org. Chem.* 2011, 76, 5867–5872

Scheme 1. Plausible Mechanism for the One-Pot Formation of the 2-Imidazolones 4[a]



[a] Notes: (a) Yield was determined by ^{1}H NMR due to contamination by tosylamide, which was formed in wet acetonitrile as a byproduct. (b) Isolated yield. (c) Determined by ^{1}H NMR.

silica gel column for chromatography. The impurities were removed by elution with EtOAc/hepthane, 1:1 followed by elution with DCM/MeOH, 9:1 to provide the target imidazol-2-one **4a**−**h**.

1,4-Dimethyl-3-phenyl-1H-imidazol-2(3H)-one (***4a***). Yield 94%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.38 (m, 2H), 7.37−7.24 (m, 3H), 6.06−5.98 (m, 1H), 3.25 (s, 3H), 1.90 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 135.2, 129.1, 127.6, 127.4, 118.6, 108.7, 30.1, 11.0; HRMS (EI) calcd for $C_{11}H_{12}ON_2$ 188.0950, found 188.0957.

1,4-Dimethyl-3-p-tolyl-1H-imidazol-2(3H)-one (***4b***). Yield 93%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 6.04−5.94 (m, 1H), 3.26 (s, 3H), 2.37 (s, 3H), 1.94−1.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.3, 137.5, 132.6, 129.8, 127.3, 118.8, 108.4, 30.2, 21.1, 11.0; HRMS (EI) calcd for $C_{12}H_{14}ON_2$ 202.1106, found 202.1103.

3-(4-Methoxyphenyl)-1,4-dimethyl-1H-imidazol-2(3H)-one (***4c***). Yield 91%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.06−5.96 (m, 1H), 3.80 (s, 3H), 3.24 (s, 3H), 1.87 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.9, 153.3, 128.7, 127.9, 118.9, 114.4, 108.2, 55.4, 30.1, 10.8; HRMS (EI) calcd for $C_{12}H_{14}O_2N_2$ 218.1055, found 218.1073.

3-(4-Fluorophenyl)-1,4-dimethyl-1H-imidazol-2(3H)-one (***4d***). Yield 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.20 (m, 2H), 7.19−7.05 (m, 2H), 6.05−5.97 (m, 1H), 3.26 (s, 3H), 1.92−1.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.2, 153.2, 131.21, 131.17, 129.3, 129.2, 118.6, 116.3, 116.0, 108.7, 30.2, 10.9; HRMS (EI) calcd for $C_{11}H_{11}FON_2$ 206.0855, found 206.0869.

3-(3-Chlorophenyl)-1,4-dimethyl-1H-imidazol-2(3H)-one (***4e***). Reaction was run at 100 °C; yield 91%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.27 (m, 3H), 7.25−7.15 (m, 1H), 6.09−5.99 (m, 1H), 3.26 (s, 3H), 1.93 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 136.4, 134.6, 130.1, 127.8, 127.6, 125.6, 118.3, 109.2, 30.2, 11.1; HRMS (EI) calcd for $C_{11}H_{11}ClON_2$ 222.0560, found 222.0558.

3-Hexyl-1,4-dimethyl-1H-imidazol-2(3H)-one (***4f***). Yield 34%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90−5.84 (m, 1H), 3.57 (t, J = 7.5 Hz, 2H), 3.20 (s, 3H), 2.06−2.00 (m, 3H), 1.68−1.52 (m, 2H), 1.36−1.22 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.4, 118.2, 107.3, 41.1, 31.4, 29.9, 29.6, 26.4, 22.5, 14.0, 10.2; HRMS (EI) calcd for $C_{11}H_{20}ON_2$ 196.1576, found 196.1569.

3-Benzyl-1,4-dimethyl-1H-imidazol-2(3H)-one (***4g***). Yield 32%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.10 (m, 5H), 5.95−5.84 (m, 1H), 4.83 (s, 2H), 3.25 (s, 3H), 1.94−1.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 137.7, 128.6, 127.3, 127.0, 118.6, 107.7, 44.5, 30.2, 10.4; HRMS (EI) calcd for $C_{12}H_{14}ON_2$ 202.1106, found 202.1107.

1,4-Dimethyl-3-tosyl-1H-imidazol-2(3H)-one (***4h***). Yield 66%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.92−5.86 (m, 1H), 3.05 (s, 3H), 2.41 (s, 3H), 2.30−2.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.0, 145.3, 135.5, 129.7, 128.0, 118.4, 111.8, 29.9, 21.7, 13.1; HRMS (EI) calcd for $C_{12}H_{14}O_3N_2S$ 266.0725, found 266.0728.

General Procedure for the Synthesis of the Tetrasubstituted Imidazol-2-ones 4i−t via One-Pot Acylation, Ag(I)-Catalyzed Cycloisomerization. To a solution of propargylamine **1b**−**f** (0.33 mmol) in dry toluene (2.5 mL) was added the appropriate isocyanate **2a**−**d** (0.4 mmol). The glass tube with reaction mixture was degassed and flushed with argon. After 1 h of heating at 110 °C, silver triflate (17 mg, 0.07 mmol) was added, and the reaction mixture was sealed and stirred for 2 h at 110 °C. The resulting reaction mixture was cooled to ambient temperature and subjected to the column chromatography with (EtOAc-/hepthane, 1:1) to afford imidazol-2-one **4i**−**t**.

1,4-Dibenzyl-3-phenyl-5-propyl-1H-imidazol-2(3H)-one (***4i***). Yield 72%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.20 (m, 8H), 7.18−7.05 (m, 5H), 6.90−6.78 (m, 2H), 4.95 (s, 2H), 3.67 (s, 2H), 2.31 (t, J = 7.8 Hz, 2H), 1.46−1.29 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.6, 138.3, 138.0, 135.3, 128.9, 128.7, 128.3, 128.0, 127.9, 127.6, 127.4, 127.0, 126.3, 120.6, 117.0, 44.8, 29.4, 25.6, 23.1, 13.9; HRMS (EI) calcd for $C_{26}H_{26}ON_2$ 382.2045, found 382.2049.

1,4-Dibenzyl-3-(4-methoxyphenyl)-5-propyl-1H-imidazol-2(3H)-one (***4j***). Yield 53%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.24 (m, 5H), 7.21−7.11 (m, 3H), 7.00 (d, J = 8.9 Hz, 2H), 6.91−6.84 (m, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.96 (s, 2H), 3.78 (s, 3H), 3.65 (s, 2H), 2.31 (t, J = 7.9 Hz, 2H), 1.47−1.30 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 153.8, 138.4, 138.1, 129.3, 128.7, 128.3, 128.1, 127.9, 127.3, 127.0, 126.3, 120.2, 117.4, 114.2, 55.5, 44.8, 29.4, 25.6, 23.1, 13.9; HRMS (EI) calcd for $C_{27}H_{28}O_2N_2$ 412.2151, found 412.2157.

1,4-Dibenzyl-3-(4-fluorophenyl)-5-propyl-1H-imidazol-2(3H)-one (***4k***). Yield 71%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.22 (m, 5H), 7.20−7.08 (m, 3H), 7.07−6.89 (m, 4H), 6.88−6.79 (m, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.95 (s, 2H), 3.65 (s, 2H), 2.32 (t, J = 7.8 Hz, 2H), 1.48−1.31 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.2, 153.6, 138.0, 137.8, 131.3, 131.2, 129.9, 129.8, 128.7, 128.4, 127.8, 127.5, 126.9, 126.4, 120.7, 117.0, 116.0, 115.7, 44.9, 29.4, 25.6, 23.2, 13.9; HRMS (EI) calcd for $C_{26}H_{25}ON_2F$ 400.1951, found 400.1953.

4-Ethyl-3-(4-methoxybenzyl)-1-phenyl-5-(thiophen-3-ylmethyl)-1H-imidazol-2(3H)-one (***4l***). Yield 50%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.24 (m, 5H), 7.19−7.13 (m, 3H), 6.90 (d, J = 8.6 Hz, 2H), 6.68−6.64 (m, 1H), 6.61−6.57 (m, 1H), 4.91 (s, 2H), 3.82 (s, 3H), 3.67 (s, 2H), 2.43 (q, J = 7.5 Hz, 2H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.9, 153.4, 138.9, 135.3, 130.1, 128.9, 128.5,

127.8, 127.6, 127.5, 125.6, 121.4, 121.1, 116.4, 114.0, 55.3, 44.2, 24.3, 16.8, 14.5; HRMS (EI) calcd for $C_{24}H_{24}O_2N_2S$ 404.1558, found 404.1574.

4-Ethyl-1-(4-fluorophenyl)-3-(4-methoxybenzyl)-5-(thiophen-3-ylmethyl)-1H-imidazol-2(3H)-one (**4m**). Yield 58%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, J = 8.5 Hz, 2H), 7.18−6.95 (m, 5H), 6.87 (d, J = 8.5 Hz, 2H), 6.67−6.61 (m, 1H), 6.60−6.53 (m, 1H), 4.88 (s, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.41 (q, J = 7.5 Hz, 2H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.1, 159.0, 153.5, 138.8, 131.30, 131.26, 130.0, 129.7, 129.6, 128.4, 127.4, 125.8, 121.5, 121.1, 116.3, 116.0, 115.7, 114.1, 55.3, 44.2, 24.3, 16.8, 14.5; HRMS (EI) calcd for $C_{24}H_{23}O_2N_2FS$ 422.1464, found 422.1468.

4-Benzyl-5-isobutyl-3-phenyl-1-propyl-1H-imidazol-2(3H)-one (**4n**). Yield 33%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.23 (m, 3H), 7.19−7.11 (m, 3H), 7.10−7.04 (m, 2H), 6.90−6.82 (m, 2H), 3.71 (s, 2H), 3.66 (t, J = 7.6 Hz, 2H), 2.37 (d, J = 7.5 Hz, 2H), 1.93−1.74 (m, 3H), 1.04−0.95 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 138.4, 135.4, 128.8, 128.2, 128.0, 127.8, 127.4, 126.2, 119.6, 117.1, 43.2, 32.5, 29.5, 28.8, 22.8, 22.4, 11.4; HRMS (EI) calcd for $C_{23}H_{28}ON_2$ 348.2202, found 348.2195.

4-Benzyl-3-(4-fluorophenyl)-5-isobutyl-1-propyl-1H-imidazol-2(3H)-one (**4o**). Yield 32%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20−7.11 (m, 3H), 7.04−6.91 (m, 4H), 6.89−6.82 (m, 2H), 3.71−3.60 (m, 4H), 2.38 (d, J = 7.4 Hz, 2H), 1.94−1.73 (m, 3H), 1.05−0.94 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 160.1, 153.2, 138.1, 131.33, 131.29, 129.8, 129.7, 128.3, 127.8, 126.3, 119.7, 117.1, 115.8, 115.5, 43.2, 32.5, 29.5, 28.9, 22.8, 22.4, 11.3; HRMS (EI) calcd for $C_{23}H_{27}ON_2F$ 366.2107, found 366.2101.

4-Butyl-1-(4-methoxybenzyl)-5-propyl-3-p-tolyl-1H-imidazol-2(3H)-one (**4p**). Yield 25%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.18 (m, 6H), 6.87 (d, J = 8.6 Hz, 2H), 4.85 (s, 2H), 3.81 (s, 3H), 2.40 (s, 3H), 2.35−2.25 (m, 4H), 1.47−1.36 (m, 2H), 1.18−1.08 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H), 0.75 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 153.6, 137.3, 133.2, 130.4, 129.7, 128.4, 127.5, 118.9, 118.6, 114.0, 55.3, 44.2, 31.1, 25.5, 23.2, 23.0, 22.1, 21.1, 13.9, 13.6; HRMS (EI) calcd for $C_{25}H_{32}O_2N_2$ 392.2464, found 392.2449.

4-Butyl-3-(4-fluorophenyl)-1-(4-methoxybenzyl)-5-propyl-1H-imidazol-2(3H)-one (**4q**). Yield 21%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.29 (m, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.18−7.12 (m, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.83 (s, 2H), 3.81 (s, 3H), 2.36−2.25 (m, 4H), 1.48−1.36 (m, 2H), 1.18−1.07 (m, 4H), 0.93 (t, J = 7.3 Hz, 3H), 0.75 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.1, 158.9, 153.5, 131.80, 131.76, 130.1, 129.5, 129.4, 128.4, 119.0, 118.7, 116.2, 115.9, 114.0, 55.3, 44.2, 31.1, 25.4, 23.2, 23.0, 22.1, 13.9, 13.6; HRMS (EI) calcd for $C_{24}H_{29}O_2N_2F$ 396.2213, found 396.2217.

1,4-Dibenzyl-5-(dec-9-enyl)-3-phenyl-1H-imidazol-2(3H)-one (**4r**). Yield 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.27 (m, 8H), 7.24−7.10 (m, 5H), 6.99−6.86 (m, 2H), 5.85 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.10−4.90 (m, 4H), 3.71 (s, 2H), 2.36 (t, J = 7.8 Hz, 2H), 2.18−2.03 (m, 2H), 1.47−1.18 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.5, 139.2, 138.4, 138.0, 135.3, 128.9, 128.7, 128.3, 128.0, 127.9, 127.6, 127.4, 127.0, 126.3, 120.8, 116.8, 114.2, 44.8, 33.8, 29.8, 29.4, 29.3, 29.2, 29.1, 28.9, 23.7; HRMS (EI) calcd for $C_{33}H_{38}ON_2$ 478.2984, found 478.2981.

1,4-Dibenzyl-5-(dec-9-enyl)-3-(4-fluorophenyl)-1H-imidazol-2(3H)-one (**4s**). Yield 54%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.29 (m, 5H), 7.24−7.14 (m, 3H), 7.10−6.95 (m, 4H), 6.94−6.84 (m, 2H), 5.84 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.12−4.90 (m, 4H), 3.67 (s, 2H), 2.36 (t, J = 7.8 Hz, 2H), 2.14−2.01 (m, 2H), 1.44−1.17 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.1, 153.6, 139.1, 138.1, 137.9, 131.3, 131.2, 129.9, 129.8, 128.7, 128.4, 127.8, 127.5, 127.0, 126.4, 120.9, 116.8, 116.0, 115.6, 114.2, 44.9, 33.8, 29.8, 29.4, 29.3, 29.2, 29.0, 28.9, 23.6; HRMS (EI) calcd for $C_{33}H_{37}ON_2F$ 496.2890, found 496.2876.

1,4-Dibenzyl-5-(dec-9-enyl)-3-(4-methoxyphenyl)-1H-imidazol-2(3H)-one (**4t**). Yield 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.29 (m, 5H), 7.24−7.13 (m, 3H), 7.03 (d, J = 8.8 Hz, 2H), 6.95−6.88 (m, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.84 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.08−4.92 (m, 4H), 3.80 (s, 3H), 3.66 (s, 2H), 2.34 (t, J = 7.8 Hz, 2H), 2.14−2.01 (m, 2H), 1.43−1.17 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 153.8, 139.1, 138.5, 138.1, 129.3, 128.7, 128.3, 128.1, 127.9, 127.4, 127.0, 126.3, 120.4, 117.2, 114.2, 55.5, 44.8, 33.8, 29.8, 29.4, 29.3, 29.2, 29.0, 28.9, 23.7; HRMS (EI) calcd for $C_{34}H_{40}O_2N_2$ 508.3090, found 508.3091.

Spectral Data for Isolated Propargylic Ureas 3a,g,i. *1-Methyl-3-phenyl-1-(prop-2-ynyl)urea* (**3a**). Mixture of rotamers ~9:1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.31 (m, 2H), 7.30−7.19 (m, 2H), 7.07−6.96 (m, 1H), 6.74 (bs, 1H), 4.14 (d, J = 2.1 Hz, 2H), 3.02 (s, 3H), 2.29 (t, J = 2.1 Hz, 0.9H), 2.03 (bs, 0.1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 138.9, 128.8, 123.2, 120.3, 79.0, 72.5, 37.9, 34.2; MS (CI) calcd for $C_{11}H_{12}ON_2$ 188, found 189 $[M + H]^+$.

3-Benzyl-1-methyl-1-(prop-2-ynyl)urea (**3g**). Mixture of rotamers ~9:1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.17 (m, 5H), 5.09 (t, J = 5.6 Hz, 1H), 4.40 (d, J = 5.6 Hz, 2H), 4.10 (d, J = 2.4 Hz, 2H), 2.92 (s, 3H), 2.24 (t, J = 2.4 Hz, 0.9H), 2.15 (bs, 0.1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 139.5, 128.5, 127.6, 127.2, 79.3, 72.1, 44.9, 37.8, 33.7; MS (CI) calcd for $C_{12}H_{14}ON_2$ 202, found 203 $[M + H]^+$.

1-Benzyl-3-phenyl-1-(1-phenylhex-1-yn-3-yl)urea (**3i**). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61−7.06 (m, 14H), 7.05−6.90 (m, 1H), 6.45 (bs, 1H), 5.50 (t, J = 7.7 Hz, 1H), 4.85 (d, J = 17.1 Hz, 1H), 4.54 (d, J = 17.1 Hz, 1H), 1.95−1.75 (m, 2H), 1.72−1.42 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2, 138.9, 137.6, 131.5, 129.1, 128.7, 128.31, 128.26, 128.0, 126.9, 123.0, 122.6, 119.7, 87.9, 85.2, 48.7, 48.2, 36.9, 19.6, 13.7; MS (CI) calcd for $C_{26}H_{26}ON_2$ 382, found 383 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for compounds **4a**−**t** and **3a,g,i**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: denis.ermolatev@chem.kuleuven.be; erik.vandereycken@chem.kuleuven.be.

■ ACKNOWLEDGMENT

Support was provided by the Fund for Scientific Research (FWO)−Flanders and by the Research Fund of the Katholieke Universiteit Leuven. P.V.A. is grateful to the EMECW (Triple I) for a doctoral scholarship.

■ REFERENCES

(1) (a) *Silver in Organic Chemistry*; Harmata, M., Ed.; John Wiley & Sons: Hoboken, 2010. (b) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (c) Weibel, J. M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149. (d) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodirguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174. (e) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199.

(2) For selected examples, see: (a) Luo, Y.; Pan, X.; Wu, J. *Tetrahedron Lett.* **2010**, *51*, 6646. (b) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745. (c) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (d) Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5710. (e) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (f) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564. (g) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.

(3) For selected examples, see: (a) Hansen, J. H.; Davies, H. M. L. *Chem. Sci.* **2011**, *2*, 457. (b) Davies, P. W.; Albrecht, S. J.-C.; Assanelli, G. *Org. Biomol. Chem.* **2009**, *7*, 1276. (c) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090. (d) Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 8933. (e) Dias, H. V. R.; Browning, R. G.; Richey, S. A.; Lovely, C. J. *Organometallics* **2004**, *23*, 1200. (f) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270.

(4) For selected examples, see: (a) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (b) Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395. (c) Wei, C.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, *23*, 4473.

(5) For examples of ring closure with oxygen nucleophiles, see: (a) Yamada, W.; Sugawara, Y.; Cheng, H. M.; Ikeno, T.; Yamada, T. *Eur. J. Org. Chem.* **2007**, 2604. (b) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096. (c) Ermolat′ev, D. S.; Mehta, V. P.; Van der Eycken, E. V. *Synlett* **2007**, *20*, 3117. (d) Peng, A. Y.; Ding, Y. X. *Org. Lett.* **2005**, *7*, 3299.

(6) For examples of ring closure with nitrogen nucleophiles, see: (a) Agarwal, S.; Knölker, H. J. *Org. Biomol. Chem.* **2004**, *2*, 3060. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (c) Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (d) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (e) Ye, S.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 6273. (f) Yu, X.; Yang, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 4526. (g) Ghavtadze, N.; Fröhlich, R.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2010**, 1787. (h) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (i) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856.

(7) (a) Ermolat′ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; De Keersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem., Int. Ed.* **2010**, *49*, 9465. (b) Pereshivko, O. P.; Peshkov, V. A.; Ermolat′ev, D. S.; Van Hove, S.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Synthesis* **2011**, 1587.

(8) Carling, R. W.; Moore, K. W.; Moyes, C. R.; Jones, E. A.; Bonner, K.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Fletcher, A. E.; Beer, M.; Sohal, B.; Pike, A.; Leeson, P. D. *J. Med. Chem.* **1999**, *42*, 2706.

(9) Bronson, J. J.; DenBleyker, K. L.; Falk, P. L.; Mate, R. A.; Ho, H.-T.; Pucci, M. J.; Snyder, L. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 873.

(10) (a) Congiu, C.; Cocco, M. T.; Onnis, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 989. (b) Xue, N.; Yang, X.; Wu, R.; Chen, J.; He, Q.; Yang, B.; Lu, X.; Hu, Y. *Bioorg. Med. Chem.* **2008**, *16*, 2550.

(11) Watanabe, K.; Morinaka, Y.; Hayashi, Y.; Shinoda, M.; Nishi, H.; Fukushima, N.; Watanabe, T.; Ishibashi, A.; Yuki, S.; Tanaka, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1478.

(12) Verniest, G.; Padwa, A. *Org. Lett.* **2008**, *10*, 4379.

(13) (a) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *122*, 2803. (b) Chernyak, D.; Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2010**, *352*, 961.

(14) For some recent approaches towards polysubstituted 2-imidazolones, see: (a) Zhao, B.; Du, H.; Shi, Y. J. *Org. Chem.* **2009**, *74*, 4411. (b) Lee, S.-H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *Org. Lett.* **2003**, *5*, 511. (c) Lee, S.-H.; Yoshida, K.; Matsushita, H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 8829. (d) Siamaki, A. R.; Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1135.

(15) Bariwal, J. B.; Ermolat′ev, D. S.; Van der Eycken, E. V. *Chem.—Eur. J.* **2010**, *16*, 3281.

(16) Dry solvents were used.