JOC The Journal of Organic Chemistry

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pubs.acs.org/joc

Pathways in the Degradation of Geminal Diazides

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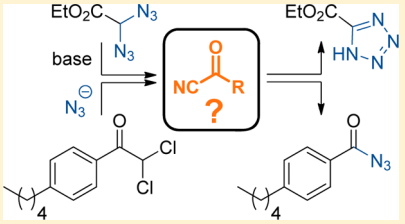
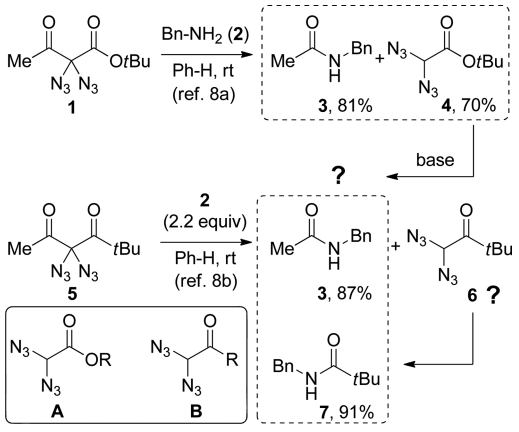
Supporting Information

ABSTRACT: The degradation of geminal diazides is described. We show that diazido acetates are converted into tetrazoles through the treatment with bases. The reaction of dichloro ketones with azide anions provides acyl azides, through in situ formation of diazido ketones. We present experimental and theoretical evidence that both fragmentations may involve the generation of acyl cyanide intermediates. The controlled degradation of terminal alkynes into amides (by loss of one carbon) or ureas (by loss of two carbons) is also shown.



Geminal diazides are a largely disregarded class of compounds.[1] Despite an inspiring report by Forster and co-workers as early as in 1908,[2] only a small number of further reports described the synthesis of geminal diazides,[3] and even less studies focused on their reactivities.[4,5] We recently launched a research program that aims to unveil new reactions with geminal diazides,[6] and we also started to reinvestigate previously reported reactions in a systematic way.[7] In the course of this program, it became apparent that geminal diazides derived from 1,3-dicarbonyls are powerful acylating agents that allow for the acylation of primary amines (Scheme 1).[8] Since we unequivocally observed the stoichiometric evolution of *tert*-butyl 2,2-diazidoacetate (**4**) using ^{1}H NMR spectroscopy when diazido acylacetate **1** reacted with primary amine **2** to give amide **3**, this acyl transfer reaction was believed to be a classical substitution: The attack of the substituting amine at the carbonyl carbon is followed by elimination of the diazido acetate leaving group **4**. In the presence of base additives, however, it was found that the diazido acetate **4** was rapidly converted, and azide functionalities have vanished completely after, for example, basic workup conditions.[8a] When studying the related acylation of amine **2** with diazido compounds derived from 1,3-diketones (e.g., **5**), the proposed diazido leaving group **6** was never detected; instead, a second acyl transfer onto the amine was observed leading to the overall formation of both amides **3** and **7**.[8b] Since little is known about the possible degradation pathways of geminal diazides,[4a−g] we then began to carefully investigate the fate of the two diazido species **A** and **B**. These diazido compounds are potentially hazardous,[9] and gaining knowledge on their reactivity and in particular on their controlled degradation is important when new methods with diazido intermediates are envisioned. The results presented in this work show how the reactive diazido compounds can be used to create challenging structural entities, such as tetrazoles and acyl azides, through novel pathways. Finally, we demonstrate that the diazide degradation can be applied to the question of how to manipulate terminal alkynes, and a novel sequence is presented that results in the controlled dismounting of the alkyne through scission of either a one-carbon or a two-carbon unit.

Scheme 1. Diazido-Containing Compounds in the Acylation of Amines

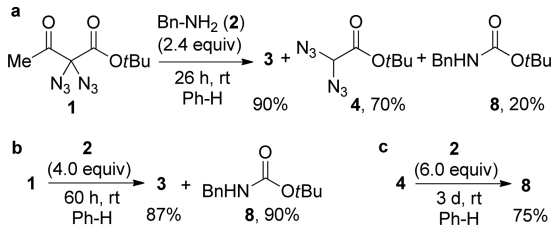


Our studies began again with diazido ester **4**, derived from the conversion of diazido acylacetate **1** with benzylamine (Scheme 2). The diazido ester **4** was readily isolated by submitting the crude reaction mixture directly onto silica for purification through flash chromatography (in up to 70% yield). The single other compound, besides the amide main product **3**, was the carbamate **8**, a compound that was formed in surprisingly inconsistent yields nevertheless, it was possible to isolate the carbamate **8** in up to 20% yield when a 2-fold excess of benzylamine was employed (see Scheme 2a). Since the

Received: April 27, 2017

DOI: 10.1021/acs.joc.7b01019
J. Org. Chem. XXXX, XXX, XXX−XXX

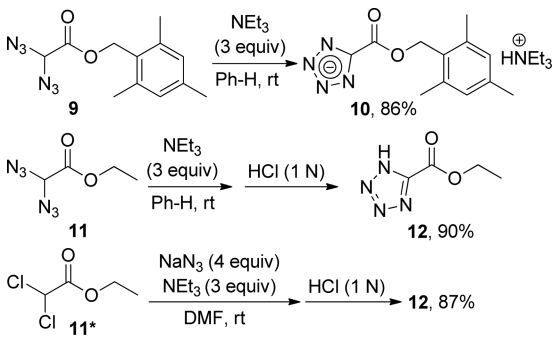
Scheme 2. Carbamate Formation from Diazido Ester 4



quantitative carbamate formation was observed with a greater excess of benzylamine and significantly lengthened reaction times (see Scheme 2b), we currently believe that the carbamate **8** is formed through the slow reaction of the diazido ester **4** with benzylamine, a rational that is fully supported by the direct reaction of isolated diazide **4** with benzylamine, resulting in unequivocal carbamate formation (see Scheme 2c).

It is important to note that NMR spectroscopy showed that diazidomethane, the formal remainder of the mass, was not formed in the course of the conversion of diazido ester **4** into carbamate **8**. Instead, the NMR data suggested the existence of a compound with a tetrazole unit that occurred to a markedly higher extent when less nucleophilic amine bases (e.g., cyclohexylamine) were employed, rather than benzylamine. This tetrazole-containing compound was, according to crude NMR data, exclusively formed when diazido ester **4** was treated with stronger bases such as DBU or NEt_3; however, its isolation failed, mainly for purification reasons. Therefore, the related diazido esters **9** and **11** were employed, and they readily yielded the expected tetrazoles **10** and **12** when treated with NEt_3 at room temperature in benzene (Scheme 3). It was possible to

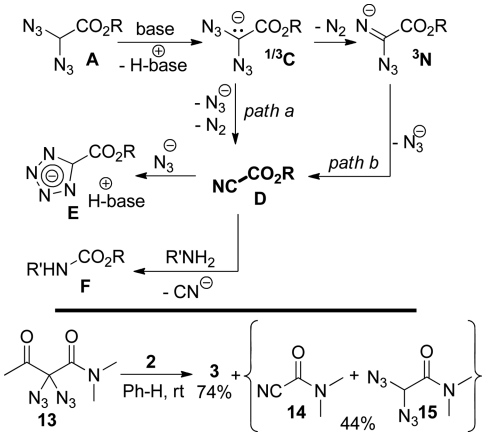
Scheme 3. Tetrazole Formation from Diazido Esters 9 and 11



cleanly isolate the ammonium salt (e.g., **10**) or, upon acidification with 1 N HCl, the neutral tetrazole (e.g., **12**).[10] Tetrazole **12** can also be isolated without the need for handling the geminal diazide **11** in a direct way; to this end, the dichloro compound **11*** was treated with a mixture of NaN_3 and NEt_3 at room temperature to give the tetrazole **12** in 87% yield.[11]

We conclude that subtle variations in basicity and nucleophilicity result in the formation of the tetrazole and the carbamate products, respectively, with bases favoring tetrazole formation and nucleophiles favoring carbamate formation. It was, at least in our hands, not possible to convert the tetrazoles into the carbamates through treatment with amines. The reactivity of diazido esters of type **A** is summarized in Scheme 4. We speculate that, in the presence of bases, deprotonation leads to the initial formation of anion **C**, a species that rapidly collapses into cyanoformate **D**. While the

Scheme 4. Proposed Mechanism for the Reactivity of Diazido Esters A



carbamate **F** is formed with nucleophilic amines through classical substitution, 1,3-dipolar cycloaddition with the azide anion results in the tetrazole **E**. Related tetrazole formations by cycloadditions were intensively studied by others,[12] including with calculations.[12d] We also observed complete and clean conversion into tetrazole **12** when stirring ethyl cyanoformate and triethylammonium azide[13] at room temperature in benzene for 20 h. Unfortunately, we lack clear experimental evidence for the in situ formation of cyanide intermediate **D**;[14] our NMR studies remain inconclusive in this regard. However, the proposed pathways via **D** are supported by three findings: (i) Calculations on the B3LYP[15]/6-311+G(2d,p)[16] level of theory including empirical dispersion[17] carried out with the Gaussian 09 program strongly suggest that, on the singlet surface, there is a concerted reaction pathway from the anion ^{1}**C** to the cyanoformate ^{1}**D** (*path a*). The corresponding transition state lies only 0.28 eV (27 kJ/mol) above the energy of the anion, hence a fast conversion is plausible (for further information including graphics, see SI). Along the calculated pathway, the loss of N_2 is directly followed by cleavage of the C–N_3 bond under formation of the cyanide and azide anion. Neither the nitrene anion (only N_2 loss) nor the carbene (only N_3^- loss) were found to be stable intermediates in a singlet state. However, the lowest triplet surface is close to the singlet surface and shows a minimum corresponding to a triplet anion ^{3}**C**. Its geometry is similar to the one of the singlet transition state and exhibits a bending of one azide group with an elongated N–N distance. On the triplet surface, the anion ^{3}**C** can decompose via a small barrier (0.15 eV) forming a stable triplet nitrene anion ^{3}**N** (through loss of N_2, *path b*). Also the carbene (N_3^- loss) is stable on the triplet surface, but high in energy (2.38 eV above the triplet anion ^{3}**C**). Because of the similarities in energy and geometry around the N–N distance of 1.4 Å, an intersystem crossing from the singlet to the triplet surface is at least plausible, and the triplet decomposition pathway via ^{3}**N** cannot be ruled out completely. (ii) A crossover experiment where a mixture of ethyl-containing diazide **11** and methyl cyanoformate was treated with triethylamine produced a mixture of the two tetrazoles, ethyl and methyl 1*H*-tetrazole-5-carboxylate, in a ratio close to 1:1 (as analyzed by LCMS). Accordingly, a pathway through the imino anion **N** followed by direct cyclization to the tetrazole appears to be less likely;[18] the cyanoformate **D** is the reasonable intermediate. (iii) The treatment of the related diazido amide **13** with benzylamine **2**

DOI: 10.1021/acs.joc.7b01019
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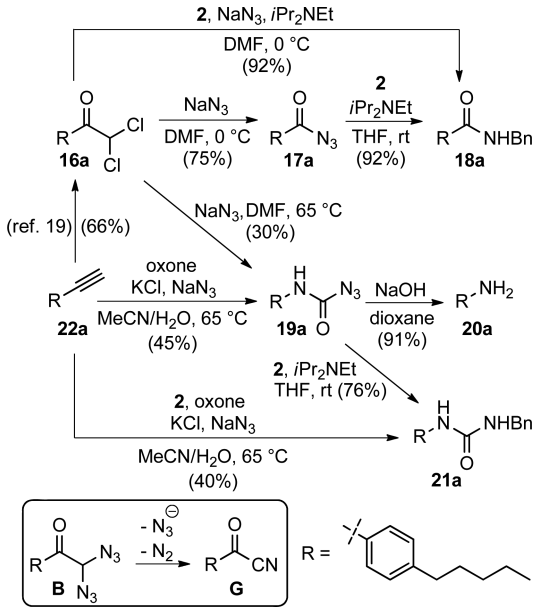
gave the expected amide **3** and an unseparable mixture of diazide **15** (^{13}C NMR: δ = 164.5, 71.5, 37.0, 36.3 ppm) and cyanide **14** (^{13}C NMR: δ = 145.0, 110.6, 38.0, 34.5 ppm).[8b]

To further elucidate the reactivity of the diazido ketones of type **B** with amines, we tried to isolate the required 2,2-diazido ketones such as, for example, **6**; unfortunately, all our attempts were not successful. Instead, acyl azides were found as the exclusive products when the corresponding 2,2-dichloro ketones were treated with an excess of azide anions. For example, dichloro compound **16a** was converted with sodium azide in DMF at 0 °C to give acyl azide **17a** in 75% isolated yield (Scheme 5). In analogy to the reactivity of the diazido

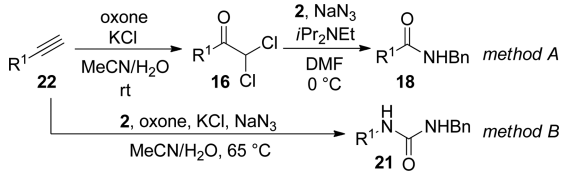
Scheme 5. Reaction Pathways of Dichloro Ketone 16a with Azides



esters discussed above, we currently believe that, under the reaction conditions, the diazido ketone **B** is generated in situ, followed by rapid fragmentation to cyanide **G**. We have shown before that acyl cyanides interconvert into acyl azides in the presence of azide anions.[8b] Acyl azide **17a** reacts smoothly with benzylamine (**2**) to provide amide **18a**, as expected. We point out that a one-pot protocol for the direct transformation of dichloro ketone **16a** into amide **18a** is also possible. Through treatment of ketone **16a** with sodium azide, benzylamine, and diisopropylethylamine in DMF at 0 °C, amide **18a** was obtained in 92% yield (Method A). As shown in Table 1, a range of dichloro ketones **16** were effectively converted into amides using this experimentally simple method. Yields were high in all cases, and various aromatic and aliphatic groups R^1 attached to the carbonyl were well tolerated. We note that a straightforward way to access the required dichloro starting materials **16** is to use the method developed by Madabhushi and co-workers[19] where terminal alkynes are treated with oxone and KCl. This highly reliable method, in combination with our amide-forming fragmentation of the dichloro ketones (Method A), represents a general approach to degrade terminal alkynes through the controlled removal of a one-carbon unit.

Since acyl azides[20] are prone to thermal decomposition producing isocyanates through Curtius rearrangement,[21] we demonstrated that, at elevated temperatures with an excess of

Table 1. Degradation of Terminal Alkynes



	substrate **22**		yield (%)[a]		
entry	R^1	no.	**16**[b]	**18**[c]	**21**[d]
1	C_6H_5	**b**	71	86	42
2	3−Cl-C_6H_4	**c**	64	93	47
3	4-MeO-C_6H_4	**d**	80[e]	88	27
4	4-Me-C_6H_4	**e**	64[e]	83	43
5	4−F-C_6H_4	**f**	80	87	41
6	3-thienyl	**g**	54	75	30
7	*n*-hexyl	**h**	58	85	31

[a]Isolated yield after chromatography. [b]Conditions: Oxone (2.0 equiv), KCl (2.0 equiv), MeCN/H_2O, rt. [c]Conditions: NaN_3 (4.0 equiv), $BnNH_2$ (1.2 equiv), $^i Pr_2NEt$ (1.2 equiv), DMF, 0 °C. [d]Conditions: Oxone (2.0 equiv), KCl (2.0 equiv), NaN_3 (3.5 equiv), $BnNH_2$ (1.2 equiv), MeCN/H_2O. [e]Conditions: NCS (2.2 equiv), $FeCl_3 \cdot 6H_2O$ (0.05 equiv), THF/H_2O, 80 °C.[23]

azide anions, the 2,2-dichloro ketone **16a** is converted into azide **19a**, a compound that was isolated in pure form (Scheme 5). As shown before by Bols and co-workers,[22] azides such as **19a** can be hydrolyzed to yield amines (e.g., **19a** → **20a** with NaOH) or reacted to ureas with amines (e.g., **19a** → **21a** with benzylamine). Futhermore, the oxyhalogenation of terminal alkyne **22a** was coupled with the degradation triggered by diazido intermediates and Curtius rearrangement. To this end, the alkyne **22a** was treated with oxone, KCl, and NaN_3 in aqueous acetonitrile at 65 °C, and the azide **19a** was obtained in acceptable 45% yield. In the presence of amine additives (e.g., **2**), it became now feasible to directly convert the terminal alkyne **22a** into the urea **21a**; the method of choice simply used the amine, oxone, KCl, and NaN_3 in aqueous acetonitrile at 65 °C (Method B). We applied this powerful method for alkyne degradation to a number of alkynes, summarized in Table 1. The method is capable of the removal of a two-carbon alkyne functionality from the precursor molecules **22** attaching a nitrogen atom at R^1 in return in moderate yields. Despite the fact that geminal diazides should be considered hazardous, the degradation methods A and B discussed above are reasonably safe and convenient, and the reactive diazido species **B** are generated in situ from dichloro precursor molecules under the present conditions. We are not aware of alternative synthesis strategies for the rapid and controlled degradation of terminal alkynes, and therefore our methods appear to fill a gap in contemporary synthetic chemistry.

In conclusion, we have shown how geminal diazides undergo degradation, most likely through initial cyanide formation. When the degradation leads to possible cyanoformate intermediates, it was found that azide addition may finally provide tetrazole products, while amine nucleophiles may create carbamate products. On the other hand, the clean degradation of geminal diazido compounds to acyl azides was also studied, a reaction that provides access to new scaffolds including amides and ureas. We believe that this deeper understanding of the diazide fragmentation pathways paves the way toward the development of new methods for the

DOI: 10.1021/acs.joc.7b01019
J. Org. Chem. XXXX, XXX, XXX−XXX

reorganization and cleavage of the carbon frameworks of organic molecules.

EXPERIMENTAL SECTION

General Remarks. The commercial reagents and solvents were used as purchased. TLC was conducted with precoated glass-backed plates (silica gel 60 F_{254}) and visualized by exposure to UV light (254 nm) or stained with ceric ammonium molybdate (CAM), basic potassium permanganate ($KMnO_4$), and subsequent heating. Flash column chromatography was performed on silica gel (40−60 μm), the eluent used is reported in the respective experiments. Abbreviations of solvents are as followed: PE: petroleum ether, EA: ethyl acetate, DCM: dichloromethane, MeOH: methanol, *i*PrOH: isopropanol. IR spectra were measured using ATR technique in the range of 400−4000 cm^{-1}. ^1H NMR spectra were recorded with 400 or 600 MHz instruments, ^{13}C NMR spectra at 101 or 151 MHz. Chemical shifts are reported in ppm relative to the solvent signal, coupling constants J in Hz. Multiplicities were defined by standard abbreviations. Low-resolution mass spectra (LRMS) were recorded using a LC/MS-combination (ESI). High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive) on a Bruker micrOTOF.

Caution! *Geminal diazides are potentially hazardous and should be handled with care.* The scale of reactions involving the use or isolation of diazido compounds was typically limited to a maximum of 0.5 mmol; additional protective gear was used with larger scales. The oily diazides were dissolved in appropriate solvents when transferred with pipettes. The heating bath of the rotary evaporator was set to 40 °C.

General Procedures. *General Procedure A for the Synthesis of 2,2-Dichloro Ketones **16**.* The alkyne **22** (1.0 equiv) was dissolved in ACN (0.4 M), and oxone (2.0 equiv) and KCl (2.0 equiv) were subsequently added. Then, water (0.8 M) was added dropwise, and the reaction mixture was stirred at 40 °C until completion of the reaction (as monitored by TLC). The mixture was diluted with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding 2,2-dichloro ketone **16**.

*General Procedure B for the Synthesis of 2,2-Dichloro Ketones **16**.* The alkyne **22** (1.0 equiv), NCS (2.2 equiv) and $FeCl_3{\cdot}6\ H_2O$ (0.05 equiv) were dissolved in THF (2.5 M) under nitrogen atmosphere, and water (0.5 M) was added. The reaction temperature was raised to 80 °C, and the mixture was stirred for 3 h. The reaction mixture was cooled to rt, quenched with aqueous saturated $NaHCO_3$ solution, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel furnished the corresponding 2,2-dichloro ketone **16**.

*General Procedure C for the Synthesis of Amides **18**.* The 2,2-dichloro ketone **16** (1.0 equiv) was dissolved in DMF (1.0 M), and the mixture was cooled to −5 °C. NaN_3 (4.0 equiv) was added, and the reaction mixture was stirred for 16 h at 0 °C. Then benzylamine (1.2 equiv) and DIPEA (1.2 equiv) were added, and the resulting mixture was stirred for additional 20 h at rt. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel furnished the corresponding amide **18**.

*General Procedure D for the Synthesis of Ureas **21**.* The alkyne **22** (1.0 equiv) was dissolved in ACN (0.4 M), and oxone (2.0 equiv) and KCl (2.0 equiv) were added. Then, water (0.8 M) was added dropwise, and the reaction mixture was stirred at 40 °C until completion of the reaction (as monitored by TLC). NaN_3 (3.5 equiv) was added, and the reaction mixture was heated to 65 °C and stirred for 16 h. Then the mixture was cooled to rt, benzylamine (1.2 equiv) was added, and the mixture was stirred for additional 20 h at rt. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding urea **21**.

*2,2-Dichloro-1-(4-pentylphenyl)ethan-1-one (**16a**).* According to the general procedure A using (0.50 g, 2.82 mmol, 1.0 equiv) 1-ethynyl-4-pentylbenzene (**22a**), 2,2-dichloro-1-(4-pentylphenyl)ethan-1-one (0.48 g, 1.86 mmol, 66%) (**16a**) was obtained after chromatography (PE:Et_2O 95:5 → 9:1) as yellow oil. TLC: R_f = 0.57 (PE:EA 8:2) [UV, $KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.04−7.97 (m, 2 H), 7.35−7.29 (m, 2 H), 6.68 (s, 1 H), 2.75−2.64 (m, 2H), 1.73−1.57 (m, 2H), 1.41−1.26 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 185.7, 150.9, 130.0, 129.1, 129.1, 67.9, 36.2, 31.5, 30.7, 22.6, 14.1. The analytical data are in agreement with previously reported ones.[19]

*2,2-Dichloro-1-phenylethan-1-one (**16b**).* According to the general procedure A using (1.00 g, 9.79 mmol, 1.0 equiv) phenylacetylene (**22b**), 2,2-dichloro-1-phenylethan-1-one (1.31 g, 6.94 mmol, 71%) (**16b**) was obtained after chromatography (PE:Et_2O 95:5 → 9:1) as colorless oil. TLC: R_f = 0.51 (PE:EA 8:2) [UV, $KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.12−8.06 (m, 2H), 7.69−7.62 (m, 1H), 7.56−7.48 (m, 2H), 6.69 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 186.0, 134.7, 131.5, 129.9 129.1, 67.9. The analytical data are in agreement with previously reported ones.[19]

*2,2-Dichloro-1-(3-chlorophenyl)ethan-1-one (**16c**).* According to the general procedure A using (0.10 g, 0.73 mmol, 1.0 equiv) 1-chloro-3-ethynylbenzene (**22c**), 2,2-dichloro-1-(3-chlorophenyl)ethan-1-one (0.10 g, 0.47 mmol, 64%) (**16c**) was obtained after chromatography (PE:Et_2O 95:5 → 9:1) as colorless oil. TLC: R_f = 0.66 (PE:EA 8:2) [UV, $KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.06 (t, J = 1.8 Hz, 1H), 7.98 (ddd, J = 7.9, 1.7, 1.1 Hz, 1H), 7.62 (ddd, J = 8.0, 2.1, 1.0 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 6.60 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 184.9, 135.44, 134.6, 132.9, 130.3, 129.9, 127.9, 67.8. The analytical data are in agreement with previously reported ones.[23]

*2,2-Dichloro-1-(4-methoxyphenyl)ethan-1-one (**16d**).* According to the general procedure B using (0.15 g, 1.10 mmol, 1.0 equiv) 1-ethynyl-4-methoxybenzene (**22d**), 2,2-dichloro-1-(4-methoxyphenyl)-ethan-1-one (0.19 g, 0.89 mmol, 80%) (**16d**) was obtained after chromatography (PE:EA 95:5 → 9:1) as colorless oil. TLC: R_f = 0.49 (PE:EA 8:2) [UV, $KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.12−8.03 (m, 2H), 7.02−6.94 (m, 2H), 6.64 (s, 1H), 3.90 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 184.7, 164.8, 132.4, 124.1, 114.4, 68.0, 55.8. The analytical data are in agreement with previously reported ones.[24]

*2,2-Dichloro-1-(p-tolyl)ethan-1-one (**16e**).* According to the general procedure A using (0.50 g, 4.22 mmol, 1.0 equiv) 1-ethynyl-4-methlbenzene (**22e**), 2,2-dichloro-1-(*p*-tolyl)ethan-1-one (0.58 g, 2.83 mmol, 67%) (**16e**) was obtained after chromatography (PE:Et_2O 95:5 → 9:1) as colorless oil. TLC: R_f = 0.62 (PE:EA 8:2) [UV, $KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.98 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.67 (s, 1H), 2.44 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 185.7, 145.9, 129.9, 129.8, 128.9, 67.9, 21.9.The analytical data are in agreement with previously reported ones.[19]

*2,2-Dichloro-1-(4-fluorophenyl)ethan-1-one (**16f**).* According to the general procedure A using (0.50 g, 4.08 mmol, 1.0 equiv) 1-ethynyl-4-fluorobenzene (**22f**), 2,2-dichloro-1-(4-fluorophenyl)ethan-1-one (0.69 g, 3.33 mmol, 82%) (**16f**) was obtained after chromatography (PE:Et_2O 95:5 → 9:1) as colorless oil. TLC: R_f = 0.56 (PE:EA 8:2) [UV, $KMnO_4$]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.20−8.10 (m, 2H), 7.23−7.15 (m, 2H), 6.61 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 184.7, 167.9, 165.3, 132.9 (d, J = 9.6 Hz), 127.7 (d, J = 3.1 Hz), 116.4 (d, J = 22.1 Hz), 67.9. The analytical data are in agreement with previously reported ones.[24]

*2,2-Dichloro-1-(thiophen-3-yl)ethan-1-one (**16g**).* According to the general procedure B using (0.20 g, 1.78 mmol, 1.0 equiv) 3-ethynylthiophene (**22g**), 2,2-dichloro-1-(thiophen-3-yl)ethan-1-one (0.19 g, 0.96 mmol, 54%) (**16g**) was obtained after chromatography (PE:Et_2O 95:5 → 9:1) as colorless oil. TLC: R_f = 0.52 (PE:EA 8:2) [UV]. ^1H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.38 (dd, J = 2.9, 1.3 Hz, 1H), 7.67 (dd, J = 5.2, 1.3 Hz, 1H), 7.38 (dd, J = 5.2, 2.9 Hz, 1H),

DOI: 10.1021/acs.joc.7b01019
J. Org. Chem. XXXX, XXX, XXX−XXX

6.43 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 180.7, 135.6, 135.1, 128.1, 126.9, 68.7. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3107, 3003, 2926, 1687, 1506, 1411, 1223, 1203, 819, 714, 615. LRMS (EI): [m/z] 194 (1) [M-H$^+$], 131 (7), 111 (100), 83 (25). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_6H_5Cl_2OS$ 194.9438; found 194.9433.

*1,1-Dichlorooctan-2-one (**16h**).* According to the general procedure A using (0.50 g, 4.45 mmol, 1.0 equiv) oct-1-yne (**22h**), 1,1-dichlorooctan-2-one (0.51 g, 2.59 mmol, 58%) (**16h**) was obtained after chromatography (PE:Et_2O 95:5) as colorless oil. TLC: R_f = 0.54 (PE:EA 8:2) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.80 (s, 1H), 2.80 (t, J = 7.3 Hz, 2H), 1.73−1.60 (m, 2H), 1.40−1.24 (m, 6H), 0.94−0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 197.5, 70.1, 35.1, 31.6, 28.7, 23.9, 22.6, 14.1. The analytical data are in agreement with previously reported ones.[19]

*N-Benzyl-4-pentylbenzamide (**18a**).* According to the general procedure C using 2,2-dichloro-1-(4-pentylphenyl)ethan-1-one (0.23 g, 0.89 mmol, 1.0 equiv) (**16a**), *N*-benzyl-4-pentylbenzamide (0.23 g, 0.82 mmol, 92%) (**18a**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.50 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.74−7.67 (m, 2H), 7.38−7.32 (m, 4H), 7.32−7.27 (m, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.36 (s, 1H), 4.65 (d, J = 5.7 Hz, 2H), 2.71−2.59 (m, 2H), 1.67−1.57 (m, 3H), 1.39−1.25 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 167.4, 147.1, 138.5, 131.9, 128.9, 128.7, 128.1, 127.7, 127.1, 44.2, 35.9, 31.5, 31.0, 22.6, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3317, 3066, 3059, 3027, 2950, 2925, 2854, 1638, 1609, 1548, 1312, 854. LRMS (ESI): [m/z] 282 (34) [M + H$^+$]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{23}NNaO$: 304.1672; found 304.1670.

*N-Benzylbenzamide (**18b**).* According to the general procedure C using 2,2-dichloro-1-phenylethan-1-one (0.50 g, 2.64 mmol, 1.0 equiv) (**16b**), *N*-benzylbenzamide (0.48 g, 2.27 mmol, 86%) (**18b**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.42 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.83−7.75 (m, 2H), 7.53−7.47 (m, 1H), 7.46−7.39 (m, 2H), 7.35 (d, J = 4.4 Hz, 4H), 7.33−7.27 (m, 1H), 6.50 (s, 1H), 4.64 (d, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 167.5, 138.3, 134.5, 131.7, 128.9, 128.7, 128.0, 127.8, 127.1, 44.3. The analytical data are in agreement with previously reported ones.[25]

*N-Benzyl-3-chlorobenzamide (**18c**).* According to the general procedure C using 2,2-dichloro-1-(3-chlorophenylethan-1-one (73 mg, 0.33 mmol, 1.0 equiv) (**16c**), *N*-benzyl-3-chlorobenzamide (75 mg, 0.31 mmol, 93%) (**18c**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.60 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.78 (t, J = 1.8 Hz, 1H), 7.68−7.63 (m, 1H), 7.49−7.45 (m, 1H), 7.39−7.28 (m, 6H), 6.44 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 166.2, 138.0, 136.3, 134.9, 131.7, 130.1, 129.0, 128.1, 127.9, 127.5, 125.2, 44.4. The analytical data are in agreement with previously reported ones.[20c]

*N-Benzyl-4-methoxybenzamide (**18d**).* According to the general procedure C using 2,2-dichloro-1-(4-methoxyphenylethan-1-one (0.15 g, 0.68 mmol, 1.0 equiv) (**16d**), *N*-benzyl-4-methoxybenzamide (0.15 mg, 0.61 mmol, 88%) (**18d**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.33 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.81−7.72 (m, 2H), 7.38−7.32 (m, 4H), 7.33−7.27 (m, 1H), 6.96−6.86 (m, 2H), 6.40 (s, 1H), 4.62 (d, J = 5.7 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 166.9, 162.4, 138.6, 128.9, 128.9, 128.0, 127.7, 126.8, 113.9, 55.5, 44.2. The analytical data are in agreement with previously reported ones.[26]

*N-Benzyl-4-methylbenzamide (**18e**).* According to the general procedure C using 2,2-dichloro-1-(4-methylphenylethan-1-one (0.30 g, 1.48 mmol, 1.0 equiv) (**16e**), *N*-benzyl-4-methylbenzamide (0.28 mg, 1.22 mmol, 83%) (**18e**) was obtained after chromatography (PE:EA 8:2 → 6:4) as white solid. TLC: R_f = 0.62 (PE:EA 1:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.72−7.65 (m, 2H), 7.39−7.33 (m, 4H), 7.33−7.27 (m, 1H), 7.22 (dd, J = 8.5, 0.6 Hz, 2H), 6.40 (s, 1H), 4.64 (d, J = 5.7 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 167.4, 142.1, 138.5, 131.7, 129.4, 128.9, 128.1, 127.7, 127.1, 44.2, 21.6. The analytical data are in agreement with previously reported ones.[26]

*N-Benzyl-4-fluorobenzamide (**18f**).* According to the general procedure C using 2,2-dichloro-1-(4-fluorophenylethan-1-one (0.30 g, 1.45 mmol, 1.0 equiv) (**16f**), *N*-benzyl-4-fluorobenzamide (0.29 mg, 1.26 mmol, 87%) (**18f**) was obtained after chromatography (PE:EA 8:2 → 6:4) as white solid. TLC: R_f = 0.61 (PE:EA 1:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.88−7.73 (m, 2H), 7.40−7.27 (m, 5H), 7.16−7.05 (m, 2H), 6.39 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 166.42, 164.9 (d, J = 252 Hz), 138.2, 130.7 (d, J = 3.2 Hz), 129.4 (d, J = 8.9 Hz), 128.9, 128.1, 127.9, 115.8 (d, J = 21.9 Hz), 44.4. The analytical data are in agreement with previously reported ones.[27]

*N-Benzylthiophene-3-carboxamide (**18g**).* According to the general procedure C using 2,2-dichloro-1-(thiophen-3-yl)ethan-1-one (0.25 g, 1.28 mmol, 1.0 equiv) (**16g**), *N*-benzylthiophene-3-carboxamide (0.21 mg, 0.96 mmol, 75%) (**18g**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.34 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.88−7.86 (m, 1H), 7.39 (dd, J = 5.1, 1.3 Hz, 1H), 7.35−7.30 (m, 6H), 6.46 (s, 1H), 4.59 (d, J = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 163.1, 138.4, 137.5, 128.9, 128.5, 128.0, 127.7, 126.6, 126.2, 43.9. The analytical data are in agreement with previously reported ones.[26]

*N-Benzylheptanamide (**18h**).* According to the general procedure C using 1,1-dichlorooctan-2-one (0.20 g, 1.01 mmol, 1.0 equiv) (**16h**), *N*-benzylheptanamide (0.19 mg, 0.87 mmol, 85%) (**18h**) was obtained after chromatography (PE:EA 8:2 → 1:1) as white solid. TLC: R_f = 0.42 (PE:EA 1:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36−7.30 (m, 2H), 7.30−7.24 (m, 3H), 5.76 (s, 1H), 4.43 (d, J = 5.7 Hz, 2H), 2.25−2.16 (m, 2H), 1.70−1.60 (m, 2H), 1.38−1.23 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 173.1, 138.6, 128.8, 127.9, 127.6, 43.7, 36.95, 31.7, 29.1, 25.9, 22.6, 14.1. The analytical data are in agreement with previously reported ones.[28]

*1-Benzyl-3-(4-pentylphenyl)urea (**21a**).* According to the general procedure D using (0.20 g, 1.13 mmol, 1.0 equiv) 1-ethynyl-4-pentylbenzene (**22a**), 1-benzyl-3-(4-pentylphenyl)urea (0.13 g, 0.45 mmol, 40%) (**21a**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.32 (DCM:MeOH 99:1) [UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.33−7.19 (m, 5H), 7.16−7.11 (m, 2H), 7.09−7.04 (m, 2H), 6.68 (s, 1H), 5.37 (t, J = 5.6 Hz, 1H), 4.36 (d, J = 5.8 Hz, 2H), 2.58−2.49 (m, 2H), 1.57 (dt, J = 15.1, 7.6 Hz, 2H), 1.38−1.24 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.0, 139.4, 138.9, 135.5, 129.3, 128.6, 127.4, 127.3, 122.3, 44.3, 35.2, 31.4, 31.1, 22.5, 13.9. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3311, 3028, 2959, 2928, 2872, 2849, 1632, 1589, 1557, 1523, 1453, 1231, 696, 651, 529. LRMS (ESI): [m/z] 297 (100) [M + H$^+$]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{24}N_2NaO$: 319.1781; found 319.1784.

*1-Benzyl-3-phenylurea (**21b**).* According to the general procedure D using (1.00 g, 9.79 mmol, 1.0 equiv) phenylacetylene (**22b**), 1-benzyl-3-phenylurea (0.92 mg, 4.07 mmol, 42%) (**21b**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.39 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.52 (s, 1H), 7.44−7.37 (m, 2H), 7.37−7.28 (m, 4H), 7.28−7.18 (m, 3H), 6.89 (m, 1H), 6.59 (t, J = 5.9 Hz, 1H), 4.30 (d, J = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 155.2, 140.4, 140.3, 128.6, 128.3, 127.1, 126.7, 121.1, 117.7, 42.7. The analytical data are in agreement with previously reported ones.[29]

*1-Benzyl-3-(3-chlorophenyl)urea (**21c**).* According to the general procedure D using (0.27 g, 1.90 mmol, 1.0 equiv) 1-chloro-3-ethynylbenzene (**22c**), 1-benzyl-3-(3-chlorophenyl)urea (0.23 g, 0.88 mmol, 47%) (**21c**) was obtained after chromatography (DCM → DCM:MeOH 99:1) as white solid. TLC: R_f = 0.34 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, DMSO) δ [ppm] = 8.77 (s, 1H), 7.68 (t, J = 2.0 Hz, 1H), 7.38−7.27 (m, 4H), 7.26−7.16 (m, 3H), 6.93 (ddd, J = 7.5, 2.0, 1.4 Hz, 1H), 6.70 (t, J = 5.9 Hz, 1H), 4.30 (d, J = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ [ppm] = 154.9, 141.9,

DOI: 10.1021/acs.joc.7b01019
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140.1, 133.1, 130.2, 128.3, 127.1, 126.7, 120.6, 117.0, 116.0, 42.7. The analytical data are in agreement with previously reported ones.[30]

*1-Benzyl-3-(4-methoxyphenyl)urea (**21d**).* According to the general procedure D using (1.04 g, 7.63 mmol, 1.0 equiv) 1-ethynyl-4-methoxybenzene (**22d**), 1-benzyl-3-(4-methoxyphenyl)urea (0.52 mg, 2.04 mmol, 27%) (**21d**) was obtained after chromatography (DCM → DCM:MeOH 99:1) as white solid. TLC: R_f = 0.38 (PE:EA 1:1) [UV]. ^{1}H NMR (400 MHz, DMSO) δ [ppm] = 8.35 (s, 1H), 7.34−7.27 (m, 7H), 6.85−6.81 (m, 2H), 6.48 (t, J = 5.9 Hz, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.71 (s, 3H).^{13}C NMR (101 MHz, DMSO) δ [ppm] = 155.4, 153.9, 140.5, 133.6, 128.2, 127.1, 126.6, 119.9, 113.9, 55.1, 42.8. The analytical data are in agreement with previously reported ones.[29]

*1-Benzyl-3-(4-methylphenyl)urea (**21e**).* According to the general procedure D using (1.02 g, 8.61 mmol, 1.0 equiv) 1-ethynyl-4-methylbenzene (**22e**), 1-benzyl-3-(4-methylphenyl)urea (0.90 mg, 3.73 mmol, 43%) (**21e**) was obtained after chromatography (DCM → DCM:MeOH 99:1) as white solid. TLC: R_f = 0.22 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, DMSO) δ [ppm] = 8.39 (s, 1H), 7.39−7.19 (m, 7H), 7.02 (d, J = 8.2 Hz, 2H), 6.52 (t, J = 5.9 Hz, 1H), 4.29 (d, J = 5.9 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 155.2, 140.4, 137.8, 129.7, 128.9, 128.2, 127.1, 126.6, 117.7, 42.7, 20.2. The analytical data are in agreement with previously reported ones.[31]

*1-Benzyl-3-(4-fluorophenyl)urea (**21f**).* According to the general procedure D using (0.51 g, 4.18 mmol, 1.0 equiv) 1-ethynyl-4-fluorobenzene (**22f**), 1-benzyl-3-(4-fluorophenyl)urea (0.42 mg, 1.72 mmol, 41%) (**21f**) was obtained after chromatography (DCM → DCM:MeOH 99:1) as white solid. TLC: R_f = 0.31 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (600 MHz, DMSO) δ [ppm] = 8.56 (s, 1H), 7.43−7.39 (m, 2H), 7.35−7.28 (m, 4H), 7.26−7.22 (m, 1H), 7.08−7.03 (m, 2H), 6.58 (t, J = 5.9 Hz, 1H), 4.29 (d, J = 6.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 156.9 (d, J = 237.1 Hz), 155.2, 140.3, 136.8, 128.2, 127.1, 126.7, 119.3 (d, J = 7.6 Hz), 115.0 (d, J = 22.1 Hz), 42.7. The analytical data are in agreement with previously reported ones.[32]

*1-Benzyl-3-(thiophen-3-yl)urea (**21g**).* According to the general procedure D using (0.50 g, 4.44 mmol, 1.0 equiv) 3-ethynylthiophene (**22g**), 1-benzyl-3-(thiophen-3-yl)urea (0.31 mg, 1.33 mmol, 30%) (**21g**) was obtained after chromatography (DCM:MeOH 99:1) as white solid. TLC: R_f = 0.37 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (600 MHz, DMSO) δ [ppm] = 8.81 (s, 1H), 7.36 (dd, J = 5.1, 3.2 Hz, 1H), 7.35−7.27 (m, 4H), 7.26−7.22 (m, 1H), 7.18 (dd, J = 3.2, 1.4 Hz, 1H), 6.99 (dd, J = 5.1, 1.4 Hz, 1H), 6.56 (t, J = 6.0 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 155.0, 140.4, 138.1, 128.2, 127.0, 126.6, 124.2, 121.1, 104.5, 42.8. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3322, 3296, 3152, 3101, 3023, 2915, 2867, 1688, 1631, 1584, 153, 1260, 1222, 761, 743, 503. LRMS (ESI): [m/z] 233 (100) [M + H^+]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{12}N_2NaOS$: 255.0563; found 255.0563.

*1-Benzyl-3-hexylurea (**21h**).* According to the general procedure D using (0.50 g, 4.45 mmol, 1.0 equiv) oct-1-yne (**22h**), 1-benzyl-3-hexylurea (0.32 mg, 1.36 mmol, 31%) (**21h**) was obtained after chromatography (PE:EA 7:3 → 3:7) as white solid. TLC: R_f = 0.42 (PE:EA 1:1) [UV]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.34−7.27 (m, 2H), 7.26−7.17 (m, 3H), 6.24 (t, J = 5.8 Hz, 1H), 5.88 (t, J = 5.6 Hz, 1H), 4.19 (d, J = 6.0 Hz, 2H), 2.99 (dd, J = 12.8, 6.8 Hz, 2H), 1.39−1.33 (m, 2H), 1.31−1.21 (m, 6H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 158.0, 140.9, 128.1, 126.9, 126.4, 42.8, 30.9, 29.9, 26.0, 21.9, 13.8. The analytical data are in agreement with previously reported ones.[33]

*N-Benzylacetamide (**3**), tert-Butyl 2,2-Diazidoacetate (**4**), and tert-Butyl Benzylcarbamate (**8**).* *tert*-Butyl 2,2-diazido-3-oxobutanoate (0.50 g, 2.08 mmol, 1.0 equiv) (**1**) was dissolved in benzene (5 mL), and benzylamine (0.54 g, 5.00 mmol, 2.4 equiv) in benzene (5 mL) was added. The reaction mixture was stirred for 26 h at rt. Evaporation of the solvent under reduced pressure and flash chromatography on silica gel (EA:PE 1:9 → EA:*i*PrOH 8:2) gave *N*-benzylacetamide (0.28 g, 1.86 mmol, 90%) (**3**) and *tert*-butyl benzylcarbamate (88 mg, 0.42 mmol, 20%) (**8**) as white solids and *tert*-butyl 2,2-diazidoacetate (0.29 g, 1.46 mmol, 70%) (**4**) as colorless oil. **3**: TLC: R_f = 0.31 (DCM:MeOH 95:5) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39−7.16 (m, 5H), 6.20 (br. s., 1H), 4.37 (d, J = 5.6 Hz, 2H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 170.1, 138.4, 128.7, 127.9, 127.5, 43.7, 23.2. The analytical data are in agreement with previously reported ones.[34] **4**: TLC: R_f = 0.60 (PE:EA 9:1) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.71 (s, 1H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 164.0, 85.1, 73.9, 27.9. The analytical data are in agreement with previously reported ones.[8] **8**: TLC: R_f = 0.75 (PE:EA 7:3) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.40−7.19 (m, 5H), 4.90 (s, 1H), 4.31 (d, J = 5.5, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.0, 139.1, 128.7, 127.6, 127.4, 79.6, 44.8, 28.5. The analytical data are in agreement with previously reported ones.[35]

*N-Benzylacetamide (**3**) and tert-Butyl Benzylcarbamate (**8**).* *tert*-Butyl 2,2-diazido-3-oxobutanoate (50 mg, 0.21 mmol, 1.0 equiv) (**1**) was dissolved in benzene (1 mL), and benzylamine (90 mg, 0.83 mmol, 2.4 equiv) in benzene (1 mL) was added. The reaction mixture was stirred for 60 h at rt. Evaporation of the solvent under reduced pressure and flash chromatography on silica gel (EA:PE 1:9 → EA:*i*PrOH 8:2) gave *N*-benzylacetamide (27 mg, 0.18 mmol, 87%) (**3**) and *tert*-butyl benzylcarbamate (39 mg, 0.19 mmol, 90%) (**8**) as white solids. **3**: TLC: R_f = 0.31 (DCM:MeOH 95:5) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39−7.16 (m, 5H), 6.20 (br. s., 1H), 4.37 (d, J = 5.6 Hz, 2H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 170.1, 138.4, 128.7, 127.9, 127.5, 43.7, 23.2. The analytical data are in agreement with previously reported ones.[33] **8**: TLC: R_f = 0.75 (PE:EA 7:3) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.40−7.19 (m, 5H), 4.90 (s, 1H), 4.31 (d, J = 5.5, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.0, 139.1, 128.7, 127.6, 127.4, 79.6, 44.8, 28.5. The analytical data are in agreement with previously reported ones.[35]

*tert-Butyl Benzylcarbamate (**8**).* *tert*-Butyl 2,2-diazidoacetate (50 mg, 0.25 mmol, 1.0 equiv) (**1**) was dissolved in benzene (1.5 mL), and benzylamine (164 mg, 1.51 mmol, 6.0 equiv) in benzene (1 mL) was added. The reaction mixture was stirred for 3 d at rt. Evaporation of the solvent under reduced pressure and flash-chromatography on silica gel (EA:PE 1:9 → EA:*i*PrOH 8:2) gave *tert*-butyl benzylcarbamate (39 mg, 0.19 mmol, 75%) (**8**) as white solid. TLC: R_f = 0.75 (PE:EA 7:3) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.40−7.19 (m, 5H), 4.90 (s, 1H), 4.31 (d, J = 5.5, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.0, 139.1, 128.7, 127.6, 127.4, 79.6, 44.8, 28.5. The analytical data are in agreement with previously reported ones.[35]

*2,4,6-Trimethylbenzyl 2,2-Diazidoacetate (**9**).* 2,4,6-Trimethylbenzyl2,2-diazido-5-(4-methoxyphenyl)-3-oxopentanoate (80 mg, 0.18 mmol, 1.0 equiv) was dissolved in THF (1.0 mL, 0.1 M). Benzylamine (22 mg, 0.20 mmol, 1.1 equiv) in THF (1.0 mL) was added, and the reaction mixture was stirred at rt for 17 h, before concentrated under reduced pressure. Purification by flash-chromatography (PE:EA 95:5 →1:1) on silica gel furnished 2,4,6-trimethylbenzyl 2,2-diazidoacetate (35 mg, 0.13 mmol, 40%) (**9**) as white solid. TLC: R_f = 0.81 (PE:EA 1:1) [UV, CAM]. ^{1}H NMR (400 MHz, C_6D_6) δ [ppm] = 6.65 (s, 2H), 5.03 (s, 2H), 4.04 (s, 1H), 2.16 (s, 6H), 2.04 (s, 3H).^{13}C NMR (101 MHz, C_6D_6) δ [ppm] = 165.3, 139.1, 138.4, 129.5, 128.2, 73.6, 63.4, 20.9, 19.4. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3007, 2918, 2865, 2107, 1736, 1456, 1312, 1243, 1192, 997, 859, 553. LRMS (ESI): [m/z] 297 (6) [M + Na^+]. As direct HRMS was not possible, 2,4,6-trimethylbenzyl 2,2-diazidoacetate (**9**) was converted into its bistriazole derivative **9′**: 2,4,6-Trimethylbenzyl 2,2-diazidoacetate (30 mg, 0.11 mmol, 1.0 equiv) (**9**) was dissolved in DMF (0.7 mL, 0.15 M), (+)-sodium L-ascorbate (22 mg, 0.11 mmol, 1.0 equiv), $CuSO_4{\cdot}5H_2O$ (27 mg, 0.11 mmol, 1.0 equiv), and phenylacetylene (34 mg, 0.33 mmol, 3.0 equiv) were added, and the reaction mixture was stirred for 3 d at rt. The mixture was chromatographed over silica gel (PE:EA 9:1 →1:1) to give 2,4,6-trimethylbenzyl 2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)-acetate (45 mg, 0.09 mmol, 86%) (**9′**) as white solid. TLC: R_f = 0.18 (PE:EA 8:2) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.19 (s, 2H), 7.85−7.77 (m, 4H), 7.70 (s, 1H), 7.47−7.39 (m, 4H), 7.39−7.32 (m, 2H), 6.84 (s, 2H), 5.47 (s, 2H), 2.27 (s, 6H), 2.25 (s, 3H).

DOI: 10.1021/acs.joc.7b01019
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^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 162.3, 149.0, 139.6, 138.7, 129.6, 129.4, 129.1, 128.9, 127.0, 126.1, 120.3, 70.9, 65.2, 21.2, 19.5. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3126, 3084, 2963, 2921, 2853, 1768, 1614, 1426, 1244, 828, 745. LRMS (ESI): [m/z] 479 (57) [M + H^+]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{28}H_{26}N_6NaO_2$: 501.2009; found 501.2009.

*Triethylammonium 5-(((2,4,6-trimethylbenzyl)oxy)carbonyl)-tetrazol-1-ide (**10**).* 2,4,6-Trimethylbenzyl 2,2-diazidoacetate (0.11 g, 0.42 mmol, 1.0 equiv) (**9**) was dissolved in benzene (0.85 mL, 0.5 M). Triethylamine (0.13 g, 1.25 mmol, 3.0 equiv) was added, and the reaction mixture was stirred at rt for 3 d. The white precipitate was filtered, washed with benzene, and dried under vacuum to obtain triethylammonium 5-(((2,4,6-trimethylbenzyl)oxy)carbonyl)tetrazol-1-ide (0.13 g, 0.38 mmol, 91%) (**10**). ^{1}H NMR (400 MHz, DMSO) δ [ppm] = 9.00 (s, 1H), 6.89 (s, 2H), 5.28 (s, 2H), 3.09 (q, J = 7.3 Hz, 6H), 2.33 (s, 6H), 2.23 (s, 3H), 1.17 (t, J = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, DMSO) δ [ppm] = 161.6, 154.9, 137.8, 137.5, 129.4, 128.6, 60.1, 45.8, 20.6, 19.1, 8.6. For further analytics, the salt **10** was converted into the free 2,4,6-trimethylbenzyl 1H-tetrazole-5-carboxylate (**10′**): Triethylammonium 5-(((2,4,6-trimethylbenzyl)oxy)-carbonyl)tetrazol-1-ide (0.13 g, 0.38 mmol, 1.0 equiv) (**10**) was dissolved in water. Aqueous HCl (1.0 M) was added (until pH < 7), and the mixture was extracted with EA. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. 2,4,6-Trimethylbenzyl 1H-tetrazole-5-carboxylate (88 mg, 0.36 mmol, 86%) (**10′**) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.77 (s, 2H), 5.47 (s, 2H), 2.29 (s, 6H), 2.22 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 156.4, 151.1, 139.5, 138.4, 129.3, 127.0, 63.9, 21.1, 19.5. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3101, 2919, 2731, 2253, 1741, 1613, 1200, 906, 852, 762. LRMS (ESI): [m/z] 269 (51) [M + Na^+]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{14}N_4NaO_2$: 269.1009; found 269.1007.

*Ethyl 2,2-Diazidoacetate (**11**).* Ethyl 2,2-diazido-3-oxobutanoate (0.35 g, 1.64 mmol, 1.0 equiv) was dissolved in THF (10 mL, 0.1 M). Benzylamine (0.20 g, 1.80 mmol, 1.1 equiv) in THF (6.0 mL) was added, and the reaction mixture was stirred at rt for 18 h, before concentrated under reduced pressure. Purification by flash chromatography (PE:EA 95:5) on silica gel furnished ethyl 2,2-diazidoacetate (0.15 g, 0.88 mmol, 54%) (**11**) as colorless oil. TLC: R_f = 0.59 (PE:EA 8:2) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.85 (s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 165.2, 73.6, 63.3, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2987, 2102, 1749, 1394, 1189, 1020, 915, 555. As direct HRMS and LRMS was not possible, ethyl 2,2-diazidoacetate (**11**) was converted into its bistriazole derivative **11′**: Ethyl 2,2-diazidoacetate (30 mg, 0.18 mmol, 1.0 equiv) (**11**) was dissolved in DMF (1.2 mL, 0.15 M), (+)-sodium L-ascorbate (35 mg, 0.18 mmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (44 mg, 0.18 mmol, 1.0 equiv), and phenylacetylene (54 mg, 0.53 mmol, 3.0 equiv) were added, and the reaction mixture was stirred for 20 h at rt. The mixture was chromatographed over silica gel (PE:EA 9:1 → 6:4) to give ethyl 2,2-bis(4-phenyl-1H-1,2,3-triazol-1-yl)acetate (59 mg, 0.16 mmol, 89%) (**11′**) as white solid. TLC: R_f = 0.43 (PE:EA 1:1) [UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.35 (s, 2H), 7.89–7.82 (m, 5H), 7.46–7.39 (m, 4H), 7.38–7.32 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 162.3, 148.9, 129.6, 129.1, 128.9, 126.1, 120.6, 70.9, 64.7, 13.9. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3130, 3102, 2981, 2969, 1760, 1457, 1427, 1371, 1282, 1209, 1019, 820, 763, 692. LRMS (ESI): [m/z] 375 (100) [M + H^+]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{20}H_{18}N_6NaO_2$: 397.1383; found 397.1384.

*Ethyl 1H-tetrazole-5-carboxylate (**12**).* Ethyl 2,2-diazidoacetate (0.15 g, 0.88 mmol, 1.0 equiv) (**11**) was dissolved in benzene (1.8 mL, 0.5 M). Triethylamine (0.27 g, 2.63 mmol, 3.0 equiv) was added and the reaction mixture was stirred at rt for 3 d. The white precipitation was filtered, washed with benzene and dissolved in water. Aqueous HCl (1.0 M) was added (until pH < 7) and the mixture was extracted with EA. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Ethyl 1*H*-tetrazole-5-carboxylate (0.11 g, 0.79 mmol, 90%) (**12**) was isolated as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 15.07 (s, 1H), 4.52 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 156.7, 151.6, 63.8, 14.0. The analytical data are in agreement with previously reported ones.[36]

*Ethyl 1H-Tetrazole-5-carboxylate (**12**).* Ethyl dichloroacetate (0.10 g, 0.63 mmol, 1.0 equiv) (**11***) was dissolved in DMF (0.63 mL, 1.0 M). NaN_3 (164 mg, 2.52 mmol, 4.0 equiv) and triethylamine (0.19 g, 1.89 mmol, 3.0 equiv) were added, and the reaction mixture was stirred at rt for 3 d. Aqueous HCl (1.0 M) was added (until pH < 7), and the mixture was extracted with EA. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Ethyl 1*H*-tetrazole-5-carboxylate (78 mg, 0.55 mmol, 87%) (**12**) was isolated as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 15.07 (s, 1H), 4.52 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 156.7, 151.6, 63.8, 14.0. The analytical data are in agreement with previously reported ones.[36]

*N-Benzylacetamide (**3**), Dimethylcarbamoyl Cyanide (**14**), and 2,2-Diazido-N,N-dimethylacetamide (**15**).* 2,2-Diazido-*N*,*N*-dimethyl-3-oxobutanamide (50 mg, 0.24 mmol, 1.0 equiv) (**13**) was dissolved in benzene (1.2 mL, 0.1 M) under nitrogen. Benzylamine (56 mg, 0.52 mmol, 2.2 equiv) (**2**) in benzene (1.2 mL) was added, and the reaction mixture was stirred at room temperature for 20 h. Evaporation of the solvent under reduced pressure and flash-chromatography on silica gel (PE:EtOAc 9:1 → EA:*i*PrOH:MeOH 5:4:1) gave a 2:1 mixture of dimethylcarbamoyl cyanide (7 mg, 0.07 mmol, 29%) (**14**) and 2,2-diazido-*N*,*N*-dimethylacetamide (6 mg, 0.04 mmol, 15%) (**15**) as colorless oil and *N*-benzylacetamide (26 mg, 0.17 mmol, 74%) (**3**) as white solid. **14**: TLC: R_f = 0.55 (PE:EtOAc 1:1) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.29 (s, 3H), 3.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 144.9, 110.6, 38.0, 34.5. The analytical data are in agreement with previously reported ones.[37] **15**: TLC: R_f = 0.55 (PE:EtOAc 1:1) [$KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.01 (s, 1H), 3.06 (s, 3H), 3.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 164.5, 71.5, 37.0, 36.3. **3**: TLC: R_f = 0.27 (DCM:MeOH 95:3) [Cl_2]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.42–7.27 (m, 5 H), 5.75 (br. s., 1 H), 4.43 (d, J = 5.6 Hz, 2 H), 2.02 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 170.0, 138.4, 128.9, 128.0, 127.7, 44.0, 23.4. The analytical data are in agreement with previously reported ones.[34]

*4-Pentylbenzoyl Azide (**17a**).* 2,2-Dichloro-1-(4-pentylphenyl)-ethan-1-one (0.20 g, 0.77 mmol, 1.0 equiv) (**16a**) was dissolved in DMF (1.0 mL, 1.0 M) and cooled to −5 °C. NaN_3 (0.20 g, 3.09 mmol, 4.0 equiv) was added, and the reaction mixture was stirred at 0 °C for 16 h. Water was added, and the mixture was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (PE:EA 98:2) gave 4-pentylbenzoyl azide (0.13 g, 0.58 mmol, 75%) (**17a**) as yellow solid. TLC: R_f = 0.63 (PE:EA 9:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 77.98–7.90 (m, 2H), 7.29–7.23 (m, 2H), 2.71–2.62 (m, 2H), 1.69–1.57 (m, 2H), 1.41–1.23 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 172.5, 150.5, 129.7, 128.9, 128.3, 36.2, 31.5, 30.8, 22.6, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957, 2929, 2858, 2350, 2130, 1689, 1602, 1236, 1174, 984, 648. LRMS (EI): [m/z] 189 (14) [M − N_2]$^+$, 132 (100), 77 (13).

*N-Benzyl-4-pentylbenzamide (**18a**).* 4-Pentylbenzoyl azide (65 mg, 0.30 mmol, 1.0 equiv) was dissolved in THF (0.3 mL, 1.0 M), and benzylamine (38 mg, 0.38 mmol, 1.2 equiv), and DIPEA (47 mg, 0.38 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 20 h at rt. Concentration under reduced pressure and purification with flash chromatography (DCM:MeOH 99:1) gave *N*-benzyl-4-pentyl-benzamide (78 mg, 0.82 mmol, 92%) (**18a**) as white solid. TLC: R_f = 0.50 (DCM:MeOH 99:1) [UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.74–7.67 (m, 2H), 7.38–7.32 (m, 4H), 7.32–7.27 (m, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.36 (s, 1H), 4.65 (d, J = 5.7 Hz, 2H), 2.71–2.59 (m, 2H), 1.67–1.57 (m, 3H), 1.39–1.25 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 167.4, 147.1, 138.5, 131.9, 128.9, 128.7, 128.1, 127.7, 127.1, 44.2, 35.9, 31.5, 31.0, 22.6, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3317, 3066, 3059, 3027, 2950, 2925, 2854, 1638, 1609, 1548, 1312, 854. LRMS (ESI): [m/z] 282 (34) [M

DOI: 10.1021/acs.joc.7b01019
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+ H$^+$]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{23}NNaO$: 304.1672; found 304.1670.

*(4-Pentylphenyl)carbamoyl Azide (**19a**).* 2,2-Dichloro-1-(4-pentylphenyl)ethan-1-one (0.10 g, 0.39 mmol, 1.0 equiv) (**16a**) was dissolved in acetonitrile (1.0 mL) and water (0.5 mL), and NaN_3 (88 mg, 1.35 mmol, 3.5 equiv) was added. The reaction mixture was stirred at 65 °C for 16 h. Water was added, and the mixture was extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (PE:EA 95:5) gave (4-pentylphenyl)carbamoyl azide (27 mg, 0.12 mmol, 30%) (**19a**) as yellow solid. TLC: R_f = 0.56 (PE:EA 8:2) [UV, CAM]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.33 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.79 (s, 1H), 2.63−2.52 (m, 2H), 1.67−1.53 (m, 2H), 1.40−1.24 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 154.0, 139.7, 134.6, 129.2, 119.5, 35.4, 31.6, 31.3, 22.7, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3316, 2953, 2926, 2858, 2139, 1680, 1543, 1241, 684, 521. LRMS (ESI): [m/z] 233 (37) [M + H$^+$]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{16}N_4NaO$: 255.1216; found 255.1215.

*(4-Pentylphenyl)carbamoyl azide (**19a**).* 1-Ethynyl-4-pentylbenzene (100 mg, 0.56 mmol, 1.0 equiv) (**22a**) was dissolved in acetonitrile (2.0 mL), and oxone (0.35 g, 1.13 mmol, 2.0 equiv) and KCl (84 mg, 1.13 mmol, 2.0 equiv) were added. Next, water (1.0 mL) was added, and the reaction mixture was stirred for 8 h at rt. NaN_3 (109 mg, 1.69 mmol, 3.0 equiv) was added, and the mixture was stirred for additional 16 h at 65 °C. Water was added, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash-chromatography on silica gel (PE:EA 95:5) gave (4-pentylphenyl)carbamoyl azide (59 mg, 0.25 mmol, 45%) (**19a**) as yellow solid. TLC: R_f = 0.56 (PE:EA 8:2) [UV, CAM]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.33 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.79 (s, 1H), 2.63−2.52 (m, 2H), 1.67−1.53 (m, 2H), 1.40−1.24 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 154.0, 139.7, 134.6, 129.2, 119.5, 35.4, 31.6, 31.3, 22.7, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3316, 2953, 2926, 2858, 2139, 1680, 1543, 1241, 684, 521. LRMS (ESI): [m/z] 233 (37) [M+H$^+$]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{16}N_4NaO$: 255.1216; found 255.1215.

*4-Pentylaniline (**20a**).* (4-Pentylphenyl)carbamoyl azide (0.12 g, 0.50 mmol, 1.0 equiv) (**19a**) was dissolved in dioxane (1.0 mL, 0.5 M), and aqueous NaOH (1.0 mL, 2.0 M) was added. The reaction mixture was stirred for 0.5 h at rt, before aqueous HCl (1.0 mL, 1.0 M) was added, and the reaction was stirred for additional 0.5 h. The mixture was diluted with aqueous NaOH and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. 4-Pentylaniline (74 mg, 0.45 mmol, 91%) (**20a**) was obtained as orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.05−6.94 (m, 2H), 6.69−6.60 (m, 2H), 3.62−3.27 (m, 2H), 2.56−2.47 (m, 2H), 1.65−1.53 (m, 2H), 1.40−1.26 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 144.1, 133.2, 129.2, 115.3, 35.2, 31.6, 22.6, 14.1. The analytical data are in agreement with previously reported ones.[38]

*1-Benzyl-3-(4-pentylphenyl)urea (**21a**).* (4-Pentylphenyl)-carbamoyl azide (0.25 g, 1.08 mmol, 1.0 equiv) (**19a**) was dissolved in THF (2.0 mL), and benzylamine (0.14 g, 1.29 mmol, 1.2 equiv) and DIPEA (0.17 g, 1.29 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 18 h at rt. Concentration under reduced pressure and purification with flash-chromatography (DCM:MeOH 99:1) gave 1-benzyl-3-(4-pentylphenyl)urea (0.24 g, 0.81 mmol, 76%) (**21a**) as white solid. TLC: R_f = 0.32 (DCM:MeOH 99:1) [UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.33−7.19 (m, 5H), 7.16−7.11 (m, 2H), 7.09−7.04 (m, 2H), 6.68 (s, 1H), 5.37 (t, J = 5.6 Hz, 1H), 4.36 (d, J = 5.8 Hz, 2H), 2.58−2.49 (m, 2H), 1.57 (dt, J = 15.1, 7.6 Hz, 2H), 1.38−1.24 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 156.0, 139.4, 138.9, 135.5, 129.3, 128.6, 127.4, 127.3, 122.3, 44.3, 35.2, 31.4, 31.1, 22.5, 13.9. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3311, 3028, 2959, 2928, 2872, 2849, 1632, 1589, 1557, 1523, 1453, 1231, 696, 651, 529. LRMS (ESI): [m/z] 297 (100) [M + H$^+$]. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{24}N_2NaO$: 319.1781; found 319.1784.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01019.

^{1}H and ^{13}C NMR spectra of selected examples, data on the crossover experiment and computational details (PDF)

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Häring, A. P.; Kirsch, S. F. *Molecules* **2015**, *20*, 20042. (b) Bräse, S.; Banert, K. *Organic azides: Syntheses and Applications*; John Wiley: Chichester, U.K., 2010. (c) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (d) Banert, K. *Synthesis* **2016**, *48*, 2361.

(2) Forster, M. O.; Fierz, H. E.; Joshua, W. P. *J. Chem. Soc., Trans.* **1908**, *93*, 1070.

(3) Recent examples: (a) Kirchmeyer, S.; Mertens, A.; Olah, G. A. *Synthesis* **1983**, *1983*, 500. (b) Kamble, D. A.; Karabal, P. U.; Chouthaiwale, P. V.; Sudalai, A. *Tetrahedron Lett.* **2012**, *53*, 4195. (c) Okamoto, N.; Sueda, T.; Minami, H.; Miwa, Y.; Yanada, R. *Org. Lett.* **2015**, *17*, 1336.

(4) Selected examples: (a) Moriarty, R. M.; Serridge, P. *J. Am. Chem. Soc.* **1971**, *93*, 1534. (b) Pearce, D. S.; Locke, M. J.; Moore, H. W. *J. Am. Chem. Soc.* **1975**, *97*, 6181. (c) Moriarty, R. M.; Bailey, B. R., III; Prakash, I. *J. Org. Chem.* **1985**, *50*, 3710. (d) Ogilvie, W.; Rank, W. *Can. J. Chem.* **1987**, *65*, 166. (e) Moriarty, R. M.; Kliegman, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 5959. (f) Barash, L.; Wasserman, E.; Yager, W. A. *J. Am. Chem. Soc.* **1967**, *89*, 3931. (g) Ranaweera, R. A. A. U.; Sankaranarayanan, J.; Casey, L.; Ault, B. S.; Gudmundsdottir, A. D. *J. Org. Chem.* **2011**, *76*, 8177. (h) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018.

(5) Selected applications: (a) Gilbert, E. E. *J. Energ. Mater.* **1987**, *5*, 77. (b) Suzuki, H.; Hwang, Y. S.; Nakaya, C.; Matano, Y. *Synthesis* **1993**, *1993*, 1218. (c) Dong, G.-X.; Li, J.-S.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1725.

(6) (a) Harschneck, T.; Hummel, S.; Kirsch, S. F.; Klahn, P. *Chem. - Eur. J.* **2012**, *18*, 1187. (b) Klahn, P.; Erhardt, H.; Kotthaus, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 7913. (c) Erhardt, H.; Häring, A. P.; Kotthaus, A.; Roggel, M.; Tong, M. L.; Biallas, P.; Jübermann, M.; Mohr, F.; Kirsch, S. F. *J. Org. Chem.* **2015**, *80*, 12460. (d) Erhardt, H.; Mohr, F.; Kirsch, S. F. *Chem. Commun.* **2016**, *52*, 545.

(7) (a) Ehrhardt, H.; Mohr, F.; Kirsch, S. F. *Eur. J. Org. Chem.* **2016**, *2016*, 5629. (b) Ehrhardt, H.; Kunz, K. A.; Kirsch, S. F. *Org. Lett.* **2017**, *19*, 178.

(8) (a) Häring, A. P.; Biallas, P.; Kirsch, S. F. *Eur. J. Org. Chem.* **2017**, *2017*, 1526. (b) Biallas, P.; Häring, A. P.; Kirsch, S. F. *Org. Biomol. Chem.* **2017**, *15*, 3184.

(9) Conrow, R. E.; Dean, W. D. *Org. Process Res. Dev.* **2008**, *12*, 1285.

(10) Recent tetrazole syntheses: (a) Zarganes-Tzitzikas, T.; Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. *Eur. J. Org. Chem.* **2015**, *2015*, 51. (b) Shmatova, O. I.; Nenajdenko, V. G. *J. Org. Chem.* **2013**, *78*, 9214. (c) Imai, T.; Harigae, R.; Moriyama, K.; Togo, H. *J. Org. Chem.* **2016**, *81*, 3975.

(11) Diazido compound **11** was isolated in 47% yield through the reaction of **11*** with NaN_3 (4 equiv) in DMF at rt.

DOI: 10.1021/acs.joc.7b01019
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(12) This cycloaddition proceeds at ambient temperature. Related tetrazole formations through reaction of organic nitriles and sodium azide typically require elevated temperatures: (a) Das, B.; Reddy, C. R.; Kumar, D. N.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, *2010*, 391. (b) Cantillo, D.; Gutmann, B.; Kappe, C. O. *J. Am. Chem. Soc.* **2011**, *133*, 4465. (c) Shie, J.-J.; Fang, J.-M. *J. Org. Chem.* **2007**, *72*, 3141. (c1) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113. (d) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 12210.
(13) Bergholz, T.; Oelkers, B.; Huber, B.; Roling, B.; Sundermeyer, J. *Chem. - Eur. J.* **2015**, *21*, 2613.
(14) The photolysis of diazido compounds was also shown to yield cyanides: Ref 4g.
(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.
(16) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724.
(17) Grimme, S. *J. Chem. Phys.* **2006**, *124*, 34108.
(18) Kraatz, U.; Hasenbrink, W.; Wamhoff, H.; Korte, F. *Chem. Ber.* **1971**, *104*, 2458.
(19) Madabhushi, S.; Jillella, R.; Mallu, K. K. R.; Godala, K. R.; Vangipuram, V. S. *Tetrahedron Lett.* **2013**, *54*, 3993.
(20) Selected syntheses of acyl acides: (a) Kim, J.-G.; Jang, O. *Synlett* **2008**, *2008*, 2072. (b) Katritzky, A. R.; Widyan, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 5802. (c) De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992. (d) Li, X.-Q.; Zhao, X. F.; Zhang, C. *Synthesis* **2008**, *2008*, 2589.
(21) Curtius, T.; Heidenreich, K. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2684.
(22) Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* **2003**, *68*, 9453.
(23) Liu, J.; Li, W.; Wang, C.; Li, Z. *Tetrahedron Lett.* **2011**, *52*, 4320.
(24) Jagdale, A. R. *Indian J. Chem.* **2009**, *48*, 1424.
(25) Nordström, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672.
(26) Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2013**, *15*, 5370.
(27) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096.
(28) Papadopoulos, G. N.; Kokotos, C. G. *J. Org. Chem.* **2016**, *81*, 7023.
(29) Zhao, J.; Li, Z.; Yan, S.; Xu, S.; Wang, M.-A.; Fu, B.; Zhang, Z. *Org. Lett.* **2016**, *18*, 1736.
(30) Basavaprabhu, H.; Sureshbabu, V. V. *Org. Biomol. Chem.* **2012**, *10*, 2528.
(31) Lin, C.-C.; Hsieh, T.-H.; Liao, P.-Y.; Liao, Z.-Y.; Chang, C.-W.; Shih, Y.-C.; Yeh, W.-H.; Chien, T.-C. *Org. Lett.* **2014**, *16*, 892.
(32) Li, F.; Sun, C.; Shan, H.; Zou, X.; Xie, J. *ChemCatChem* **2013**, *5*, 1543.
(33) Kim, S. H.; Hong, S. H. *Org. Lett.* **2016**, *18*, 212.
(34) Zeng, H.-T.; Huang, J.-M. *Org. Lett.* **2015**, *17*, 4276.
(35) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283.
(36) Aureggi, V.; Sedelmeier, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8440.
(37) Kobler, H.; Schuster, K.-H.; Simchen, G. *Justus Liebigs Ann. Chem.* **1978**, *1978*, 1946.
(38) Andersen, K. K.; Chumpradit, S.; McIntyre, D. J. *J. Org. Chem.* **1988**, *53*, 4667.

DOI: 10.1021/acs.joc.7b01019
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