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Nitrogen Heterocycles |*Hot Paper*|

Ring Opening of Donor–Acceptor Cyclopropanes with the Azide Ion: A Tool for Construction of N-Heterocycles

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Abstract: A general method for ring opening of various donor–acceptor cyclopropanes with the azide ion through an S_N2-like reaction has been developed. This highly regioselective and stereospecific process proceeds through nucleophilic attack on the more-substituted C2 atom of a cyclopropane with complete inversion of configuration at this center. Results of DFT calculations support the S_N2 mechanism and demonstrate good qualitative correlation between the relative experimental reactivity of cyclopropanes and the calculated energy barriers. The reaction provides a straightforward approach to a variety of polyfunctional azides in up to 91% yield. The high synthetic utility of these azides and the possibilities of their involvement in diversity-oriented synthesis were demonstrated by the developed multipath strategy of their transformations into five-, six-, and seven-membered N-heterocycles, as well as complex annulated compounds, including natural products and medicines such as (−)-nicotine and atorvastatin.

Introduction

The great synthetic opportunities that the azide function provides to various organic molecules allow for the synthesis of a plethora of nitrogen-containing acyclic and cyclic compounds, including physiologically active compounds.[1] The main transformations of the azido-group that are accompanied by the elimination of an N_2 molecule (such as Staudinger, Curtius, Schmidt, and Boyer reactions) can be used for the efficient formation of synthetically and biologically important compounds such as amines, imines, amides as well as various azaheterocycles.[2] Among the reactions of azides that take place without the loss of N_2, the dominant reaction is [3+2] cycloaddition of azides as dipoles to unsaturated compounds, affording triazole and tetrazole derivatives.[3] These and many other synthetic applications of alkyl, aryl, and alkenyl azides have stimulated the development of numerous methods for the preparation of these useful compounds.[4]

Herein we primarily describe a simple and efficient regio- and stereoselective synthesis of highly functionalized azides **2** through S_N2-like ring opening of donor–acceptor (D–A) cyclopropanes[5,6] **1** with the azide ion (Scheme 1a). The D–A cyclopropanes that can be involved in this reaction include aryl-, heteroaryl, and alkenyl-substituted cyclopropane-1,1-diesters, keto- and nitroesters, diketones, and dinitriles.

Curiously, S_N2-like ring opening of D–A cyclopropanes with the azide ion has not, to our knowledge, previously been studied.[7] Synthesis of γ-azidoesters by a reaction of cyclopropane hemimalonates with the azide ion has recently been reported by Kerr and co-workers.[8] However, this reaction proceeds through the initial formation of acyl azides followed by a [3,3]-sigmatropic rearrangement with intermediate ketene generation. Chandrasekaran and co-workers reported an electrophilic ring opening of 2-alkoxycyclopropanecarboxylates with the NIS/NaN_3 system, yielding γ-iodoazides.[9] Nevertheless, both methods[8,9] have significant limitations because other types of D–A cyclopropanes, including the extensively studied 2-substituted cyclopropane-1,1-diesters, were found to be unable to yield the desired azides under the conditions examined.

In contrast, our synthetic strategy, based on the stereo specific S_N2-like ring opening, allows for an impressive range of readily available starting D–A cyclopropanes to be involved in this transformation. This provides powerful access to libraries of polyfunctional azides either in racemic or in optically active forms, equipped with (hetero)aryl or alkenyl substituents at the geminal position as well as electron-withdrawing groups, such as ester, keto, nitro, and cyano groups at the γ-position.

The high synthetic utility of azides **2** can be demonstrated by their use as essential building blocks for the assembly of a broad range of skeletal diversity of N-heterocyclic systems, including natural compounds and medicines. Due to pre-installed multiple functional groups (FG) that exhibit excellent

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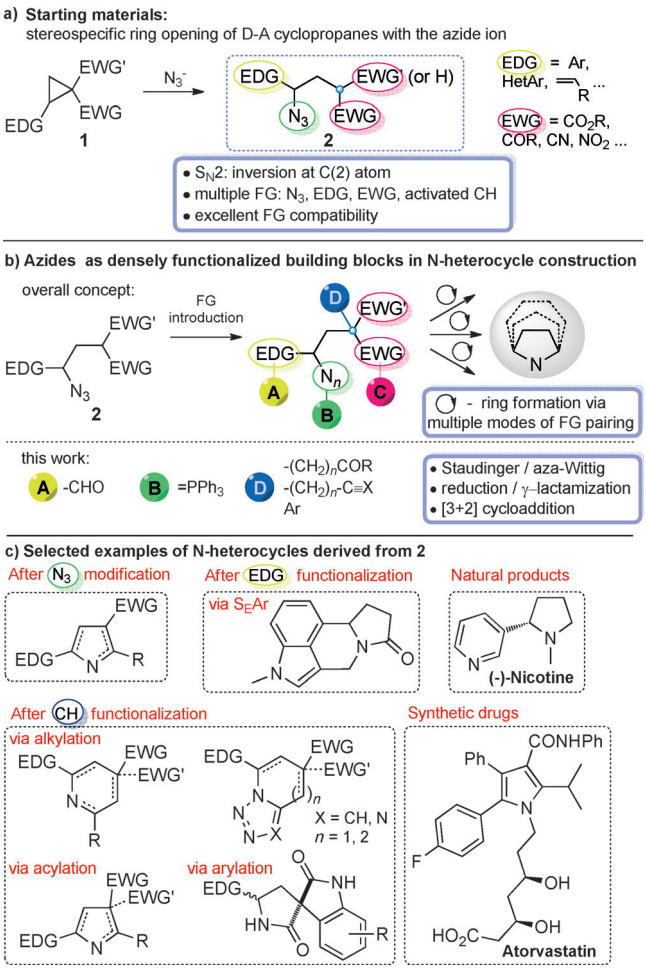


Scheme 1. General strategy used in this work.

compatibility, azides **2** are densely functionalized templates, offering promise in the design and development of novel pathways for diversity-oriented synthesis.[10]

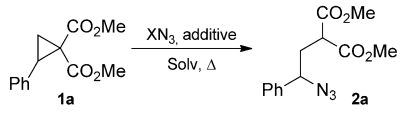
To demonstrate these possibilities, we elaborated a branching synthetic strategy for the transformation of azides **2** based on the initial introduction of a suitable FG at one or more sites of molecules **2** (electron-donating group (EDG), electron-withdrawing group (EWG), activated CH, or azide) followed by intramolecular functional group-pairing reactions (Scheme 1 b). In this work, EDG functionalization (**A**, through formylation), N_3-group modification (**B**, through reduction to amine or iminophosphorane generation), or activated CH functionalization (**D**, including alkylation, acylation, arylation) opens multiple modes for further ring formation, for example, through Staudinger/aza-Wittig reactions (azide/carbonyl groups pairing), alkylation/[3+2] cycloaddition (azide/alkyne or azide/nitrile pairing), and azide reduction/lactamization (azide/ester pairing). These sequences, involving an optional set of possible modifications of azides **2**, provide straightforward access to structures that are highly valuable in drug development, such as pyrroles, pyrrolines, pyrrolidines, pyridines, piperidines, triazoles, and tetrazoles, as well as to complex annulated and spiro-fused heterocyclic skeletons. Moreover, the present methodology was also exploited in the synthesis of natural products and synthetic drugs, such as (−)-nicotine and atorvastatin (commercially available as a calcium salt under the name Lipitor, which is a cholesterol-lowering medication that is the all-time best-selling drug around the world).

Results and Discussion

Donor–acceptor cyclopropane ring opening with the azide ion

During the search for appropriate conditions for the ring opening of D–A cyclopropanes **1** with the azide ion, we relied on critical aspects that influence efficiency in the reactions of D–A cyclopropanes as well as reactions between electrophilic cyclopropanes and nucleophiles. On the one hand, in most reactions of D–A cyclopropanes, a Lewis acid (LA) activation is required.[5,11] On the other hand, nucleophilic ring opening of activated cyclopropanes is mainly considered to be an S_N2-like process wherein the leaving group is a carbanion that is stabilized by electron-withdrawing substituent(s). In this regard, we carried out initial experiments with the model cyclopropane **1a** in the presence of a LA as an activator as well as under conditions typical for S_N2 reactions (Table 1).

Table 1. Optimization of the reaction conditions for **1a** transformation into azide **2a**.[a]



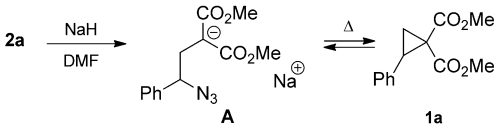
Entry	XN_3 (equiv)	Additive (equiv)	Solv	T [°C]	t [h]	Yield [%][b]
1	$TMSN_3$ (1)	–	PhCl	131	8	–
2	$TMSN_3$ (3)	TMSOTf (1.2)	PhCl	131	8	40
3	$TMSN_3$ (3)	TMSOTf (3)	PhCl	131	10	60
4	$TMSN_3$ (3)	TMSOTf (3.5)	PhCl	131	10	66
5	NaN_3 (2)	–	DMF	100	4	15
6	NaN_3 (2)	Et_3N·HCl (2)	DMF	50	4	–
7	NaN_3 (2)	Et_3N·HCl (2)	DMF	100	4	94
8	NaN_3 (1)	Et_3N·HCl (1)	DMF	100	9	90
9	NaN_3 (2)	Et_3N·HCl (2)	DMSO	100	4	92
10	NaN_3 (2)	NH_4Cl (2)	DMF	100	4	86

[a] 0.5 M solution of **1a**. [b] Yield determined by ^1H NMR spectroscopic analysis .

We started our research by using trimethylsilyl azide ($TMSN_3$), which can serve as both an activating LA and a source of the azide ion. However, no conversion of **1a** into azide **2a** was observed even under prolonged heating in PhCl (Table 1, entry 1). This result can be attributed to the low LA activity of $TMSN_3$. Indeed, the addition of TMSOTf as an activator directs this reaction to azide **2a** formation (Table 1, entries 2–4). A brief screening of the ratio of **1a** to $TMSN_3$ to TMSOTf revealed that 66% is the highest yield of **2a** that can be achieved under these conditions (Table 1, entry 4), whereas further increase in the amount of azide source and activator

loadings as well as reaction time did not lead to an increase in the yield of **2a**.

When NaN_3 in *N*,*N*-dimethylformamide (DMF), a typical system for S_N2 reaction, was used, we observed only 15% conversion of **1a** into the desired azide **2a** (Table 1, entry 5) and the ratio of **2a** to **1a** did not vary with time or with an increase in the amount of NaN_3. This result indicates the reversibility of **1a** ring opening with the azide ion, which serves as a nucleophile in the forward reaction and as a leaving group in the reverse nucleophilic substitution leading to closure of the three-membered ring. Whereas the high nucleophilicity of the azide ion is common knowledge, its ability to act as a leaving group in S_N2 reactions is a quite untypical phenomenon in organic synthesis.[12] To verify this reversibility, we treated **2a** with NaH in DMF at 100 °C (Scheme 2). After quenching, the resulting mixture was found to contain cyclopropane **1a** and azide **2a** in 85:15 ratio, which is identical to that obtained in the reaction of **1a** with NaN_3.

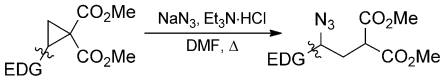


Scheme 2. Check of the reversibility of **1a** ring opening with the azide ion.

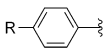
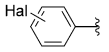
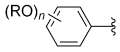
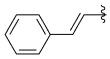
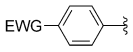
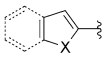
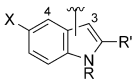
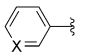
To overcome the problem of reversibility, we carried out the reaction of **1a** with NaN_3 in the presence of $Et_3N{\cdot}HCl$ (Table 1, entries 6–9), which should provide protonation of the incipient malonate anion and preclude the reverse reaction. A brief examination of variations in the loading of the nucleophile or the proton source, reaction temperature, and duration revealed that the optimal reaction conditions are heating of a mixture of **1a**, NaN_3, and $Et_3N{\cdot}HCl$ in 1:2:2 ratio in DMF at 100 °C for 4 h (Table 1, entry 7). Replacement of DMF by dimethyl sulfoxide (DMSO) did not lead to noticeable changes in the reaction efficiency, whereas the employment of NH_4Cl instead of $Et_3N{\cdot}HCl$ (Table 1, entry 10) resulted in a 10% decrease in the yield of **2a**.

With the optimized conditions in hand, we studied the scope of this reaction by using a broad range of cyclopropane-1,1-diesters **1a–z** with a wide variety of donor groups, including aryls with different electronic and steric effects, heteroaryl and alkenyl groups (Table 2). Cyclopropanes **1a–k** bearing alkyl, halogen, and alkoxy group(s) at various positions of the aromatic ring as well as heteroarene-derived cyclopropanes **1p–x** with furyl, thienyl, pyrrolyl, benzofuryl, benzothienyl, and indolyl substituents afforded the corresponding azides **2a–k** and **2p–x** in high isolated yields. It is noteworthy that pyrrolyl- and 3-indolyl-substituted cyclopropanes **1p** and **1v–x** require lower temperature for efficient conversion into azides **2**. Meanwhile, introduction of electron-withdrawing substituents onto the phenyl group, as in **1m–o**, led to some decrease in the yield of azides **2**. The same trend, namely a decrease in yield by approximately 20%, was observed for the reaction of 3-pyridyl-substituted cyclopropane **2y** and its more electron-depleted *N*-oxide derivative **2z**. The use of the ethyl ester instead of its methyl analogue, as in the case of 2-furylcyclopropane-1,1-diesters **1q** and **1q′**, did not influence the reaction yield but decelerated the process.

Table 2. Variation of the donor substituents.[a]



1a-z **2a-z**

1,2	EDG	*T* [°C]	*t* [h]	Yield [%][b]
R				
a: H		100	4	88
b: Me		100	5	81
Hal				
c: 4-F		100	8	73
d: 4-Br		100	7	78
e: 2-Br		100	10	71
$(RO)_n$				
f: 4-MeO		100	4	77
g: 2,3-$(MeO)_2$		100	4	85
h: 2-BnO-3-MeO		100	10	72
i: 3,4-$(MeO)_2$		100	5	79
j: 3,5-$(MeO)_2$		100	5.5	86
k: 3,4,5-$(MeO)_3$		100	4	75
l		100	2	80
EWG				
m: NO_2		85	24	58
n: CO_2Me		85	24	61
o: CN		100	4	53
p: 1-Me-pyrrol-2-yl		70	3	71
q:[c] 2-Fu		100	4	75
r: 2-Th		100	5	79
s: 2-benzofuryl		100	14	71
t: 2-benzothienyl		100	6	81
u: 1-Me-4-Ind		100	3	78
v: 1-Bn-3-Ind		50	3	91
w: 1-Bn-5-Cl-3-Ind		50	3	86
x: 1-Bn-2-Me-3-Ind		50	4	88
X				
y: N		100	4	83
z: N→O		100	2	61

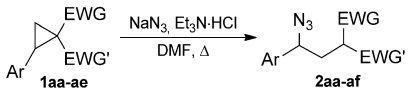
[a] Reaction conditions: 0.5 M solution of **1** in DMF, NaN_3 (2 equiv), $Et_3N{\cdot}HCl$ (2 equiv). [b] Yield of isolated product. [c] The corresponding diethyl derivative **2q′** was obtained after 10 h (100 °C) in 79% yield. Fu = furyl; Th = thienyl; Ind = indolyl.

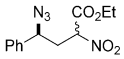
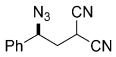
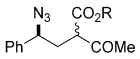
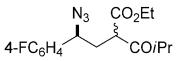
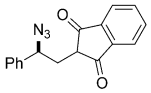
For all substrates, the reaction proceeds with exceptional regioselectivity through nucleophilic attack on the more-substituted C2 atom rather than the C3 atom. Nucleophilic ring opening of 2-alkenyl-derivative **1l** can proceed through attack on either the C2 atom of the three-membered ring (S_N2-like reaction) or the β-atom of the C=C bond (S_N2'-like reaction). We found that **1l** chemoselectively undergoes an S_N2-like reaction that furnishes azide **2l** exclusively.

The developed synthetic procedure is easily scalable without any loss of efficiency. This was demonstrated by isolation of **2a** in 85% yield when 3.35 g (14 mmol) of **1a** was used under the developed conditions.

To demonstrate the general character of the process and significantly extend the collection of densely functionalized azides, we then involved other subclasses of D–A cyclopropanes in this reaction (Table 3). Nitroester **1aa**, dinitrile **1ab**, ketoesters **1ac**–**ae**, and diketone **1af** were found to undergo efficient ring opening with the azide ion under similar reaction conditions. In all cases, higher reactivity was observed in comparison with diester **1a**. Ketoesters **1ac**–**ae** underwent full conversion into **2ac**–**ae** under heating at 90 °C in 1–4 h, whereas for nitroester **1aa** the reaction was complete after 2 h at 55 °C. Dicyanocyclopropane **1ab** and indan-1,3-dione-derived cyclopropane **1af**, which underwent easy conversion into azides **2ab** and **2af** even at room temperature, proved to be the most reactive substrates. Despite mild reaction conditions, **2ab** was isolated in only 43% yield because of formation of a complex mixture of unidentified products.

Table 3. Variation of the acceptor substituents.[a]

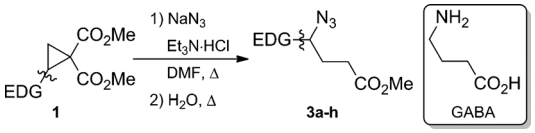


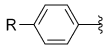
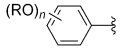
2	Azide 2	T [°C]	t [h]	Yield [%][b]
aa		55	2	76
ab[c]		25	3	43
R				
ac: Me		90	4	80
ad: Et		90	3	79
ae		90	1	90
af		25	6	85

[a] Reaction conditions: 0.5 M solution of **1** in DMF, NaN_3 (2 equiv), $Et_3N{\cdot}HCl$ (2 equiv). [b] Yield of isolated product. [c] Ratio of **1ab**/NaN_3/$Et_3N{\cdot}HCl$ = 1:1:1.

Relying on the reaction of cyclopropane diesters **1** with NaN_3, we developed a one-pot method for the preparation of 4-azido-4-(hetero)arylbutyrates **3** through cyclopropane ring opening/Krapcho dealkoxycarbonylation[17] (Table 4). The first step, a cyclopropane **1** ring opening, was carried out under the previously optimized conditions (Table 2). Next, six equivalents of water were added to the reaction mixture, which was then heated at 140 °C (Table 4). Variation of the aromatic substituents in cyclopropanes **1** had no significant influence on the reaction efficiency, except for 3-pyridyl-substituted cyclopropane **1y**. In the latter case, a complex mixture of products of dealkoxycarbonylation and N-alkylation was obtained. To prevent the side-process of N-alkylation, pyridine-*N*-oxide derivative **1z** was used, which undergoes dealkoxycarbonylation furnishing **3h** in reasonable yield.

Table 4. One-pot transformation of cyclopropane-1,1-diesters **1** into 4-azido-4-(hetero)arylbutyrates **3**.[a]



3	EDG	t [h]	Yield [%][b]
R			
a: H		15	85
b: Me		20	80
$(RO)_n$			
c: 2,3-$(MeO)_2$		28	76
d: 3,5-$(MeO)_2$		23	81
e: 3,4-$(MeO)_2$		20	71
f: 3,4,5-$(MeO)_3$		24	65
g		24	68
h[c]		12	28

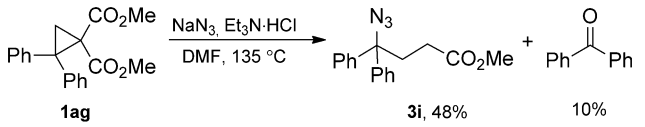
[a] Reaction conditions: 1) 0.5 M solution of **1** in DMF, NaN_3 (2 equiv), $Et_3N{\cdot}HCl$ (2 equiv); 2) H_2O (6 equiv), 140 °C. [b] Yield of isolated product. [c] Reaction conditions: 2) H_2O (6 equiv), LiCl (2 equiv), 125 °C.

This one-pot process provides a simple approach to 4-azidobutyrates **3**[18] and is a shortcut alternative to the two-step procedure reported by Kerr.[8] Compounds **3** are immediate precursors of 4-aminobutyrates, which are derivatives of γ-aminobutyric acid (GABA).[19] 4-Aminobutyrates can accentuate or attenuate neuromediatory effects of GABA and are promising compounds for the treatment of CNS-related diseases.[20] Additionally, derivatives of 4-amino-4-(hetero)arylbutyric acid are known to inhibit Src SH2[21] and aggrecanases-1 and -2,[22] as well as to exhibit other types of bioactivities.

The elaborated methodology can be used for the nucleophilic ring opening of D–A cyclopropanes with not only tertiary but also quaternary donor sites. Given that one carbon substituent serves as a leaving group, S_N2-like reactions of such cyclopropanes can be compared with nucleophilic substitutions in tertiary halides, which are considered to be

The ring opening of D–A cyclopropanes with the azide ion thus provides a straightforward general approach to various types of previously difficult to access acyclic polyfunctional compounds **2** with the strategic 1,3-relationship between N_3 and other diverse functions, such as CO_2R, COR, NO_2, and CN.[13–16] This supplies azides **2** with versatile reactivity and makes them valuable intermediates for the construction of a diverse range of molecular skeletons.

poor substrates in S_N2 processes.[23–25] Nevertheless, we succeeded in carrying out a chemoselective ring opening of cyclopropane **1 ag** (Scheme 3) through azide ion attack on the quaternary cyclopropane C2 atom. The harsher conditions that



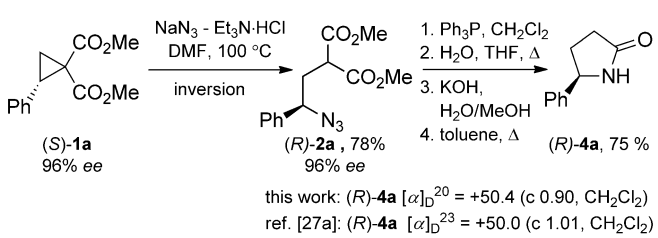
Scheme 3. Domino transformation of 2,2-diphenylcyclopropane-1,1-diester **1 ag** into azidobutyrate **3 i**.

were necessary for this transformation meant that ring opening was accompanied by dealkoxycarbonylation leading to the formation of azidobutyrate **3 i**. Unfortunately, the generation of nitrene and its subsequent rearrangements compete with the main reaction, ensuring formation of benzophenone as a side-product and isolation of **3 i** in only moderate yield.

Ring opening of optically active cyclopropane (*S*)-1a with the azide ion: Walden inversion as a support of S_N2-like mechanism

The development of a rapid synthetic access to enantiopure azides of type **2** is critically important in the context of their further employment as chiral reagents in the synthesis of biologically active compounds such as GABA-based ring structures, as well as in diversity-oriented synthesis. The D–A cyclopropane ring opening with the azide ion should provide such access because complete retention of stereo information in the reaction involving optically active cyclopropanes is expected. Moreover, the stereochemical result of this reaction allows for some insight into the mechanism of the transformation of **1** into **2**.

In this regard, we carried out an experiment with enantiopure cyclopropane (*S*)-**1 a**[26] furnishing azide **2 a** as an individual enantiomer. To determine the absolute configuration of **2 a**, it was converted into pyrrolidone **4 a** (Scheme 4), the optical rotation of which, $[\alpha]_D^T$, was previously reported for the individual enantiomers.[27] Comparison of the reported data with our results allowed us to assign **4 a** and, thus, **2 a** to *R*-enantiomers. Therefore, the transformation of **1** into **2** proceeds with full inversion of configuration at the reacting C2 atom—one of the



Scheme 4. Inversion of configuration in the nucleophilic ring opening of cyclopropane (*S*)-**1 a**.

principal characteristics of a typical S_N2 reaction. It is notable that Kerr and co-workers found total retention of absolute configuration in the reaction of NaN_3 with the cyclopropane hemimalonate. This was explained by a notably different mechanism involving an intermediate acyl azide formation and its [3,3]-sigmatropic rearrangement.[8] Therefore, in terms of stereochemistry, our method is complementary to Kerr's ring opening because the same enantiomer of a cyclopropane undergoes enantioselective ring opening by azide ion with either inversion or retention of its absolute configuration.

DFT study of the reaction mechanism and the relative reactivity of donor–acceptor cyclopropanes

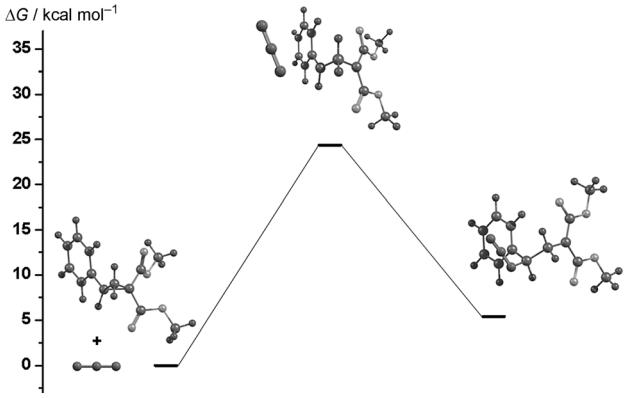
To gain a better understanding of the general reaction pattern, we carried out density functional theory (DFT) calculations of energy barriers for D–A cyclopropane ring opening with the azide ion using the B3LYP hybrid functional and the standard SVP basis set[28] implemented in the ORCA 2.9 program package.[29] The solvent effects were estimated by using the COSMO solvation model[30] with DMF as a solvent.

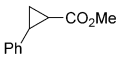
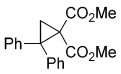
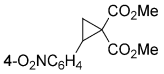
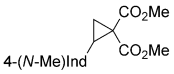
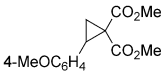
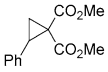
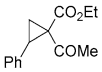
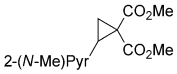
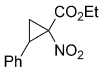
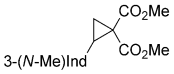
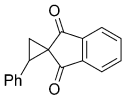
For all studied cyclopropanes **1** we localized transition states (TS) of their S_N2-like ring opening through azide ion attack onto the C2 atom. These TS are of the type found in common S_N2 reactions but they are characterized by smaller values of angle for the attack of a nucleophile (Nu). Whereas for typical S_N2 reactions the Nu-C-LG (leaving group) angle approaches 180°, for S_N2-like ring opening of D–A cyclopropanes **1 a**–**af** the angle varies from 142° to 148°. A schematic representation of the energy profile and the calculated energy barriers are given in Table 5.

The trend of variation in the calculated $\Delta G^{\neq}$ (Table 5) qualitatively coincides with the changes in reaction conditions (temperature, duration), which primarily characterize the reactivities of the D–A cyclopropanes **1** towards the azide ion. Meanwhile, both in vitro and in silico data indicate that the reactivity of **1** depends significantly on the nature of the acceptor substituents in their molecules. In particular, cyclopropane **1 ah**, which contains a single ester group as an acceptor (Table 5, entry 1), has a very high transition state energy for ring opening with the azide ion ($\Delta H^{\neq} = 28.4$, $\Delta G^{\neq} = 38.6$ kcal mol^{-1}). The presence of a second ester group (diester **1 a**) lowers the energy barrier significantly (Table 5, entry 7; $\Delta H^{\neq} = 17.6$, $\Delta G^{\neq} = 24.4$ kcal mol^{-1}), whereas an even greater decrease in the energy barrier height is observed for the cyclopropanes containing the more electron-withdrawing keto or nitro groups (Table 5, entries 8 and 10; ketoester **1 ad**, $\Delta H^{\neq} = 14.4$, $\Delta G^{\neq} = 23.1$ kcal mol^{-1}, nitroester **1 aa**, $\Delta H^{\neq} = 11.4$, $\Delta G^{\neq} = 21.0$ kcal mol^{-1}). These results correspond well with the experimental data. Namely, compound **1 ah** did not undergo ring opening even under prolonged heating to reflux in DMF (153 °C). Diester **1 a** was converted into azide **2 a** at 100 °C, whereas the transformation of ketoester **1 ad** into the corresponding azide **2 ad** required lower temperature (90 °C) and nitroester **1 aa** reacted efficiently at 55 °C.

These changes in the reactivity of D–A cyclopropanes can be qualitatively explained on the basis of the well-known

Table 5. Energy profile and energy barriers for cyclopropane **1** ring opening with the azide ion.



Entry	Cyclopropane **1**		$\Delta H^{\neq}/\Delta G^{\neq}$ [kcal mol^{-1}]	Experimental data T [°C]	t [h]
1		**1 ah**	28.4/38.6	–[a]	–[a]
2		**1 ag**	19.5/31.2	135	12
3		**1 ai**	18.9/28.8	100[b]	24[b]
4		**1 m**	15.2/26.7	85	24
5		**1 u**	16.4/26.3	100	3
6		**1 f**	15.2/25.4	100	4
7		**1 a**	17.6/24.4	100	4
8		**1 ad**	14.4/23.1	90	3
9		**1 p**	12.0/21.4	70	3
10		**1 aa**	11.4/21.0	55	2
11		**1 aj**	10.2/21.9	50[c]	3[c]
12		**1 af**	12.0/20.8	25	6
13		**1 ab**	9.1/17.7	25	3

[a] No conversion under prolonged heating at reflux (153 °C) in DMF. [b] Experimental data are for the corresponding diethyl ester.[7c] [c] Experimental data are for *N*-benzyl analogue **1 v**.

dependence of $\Delta G^{\neq}$ on $\Delta_r G$ as exemplified, for example by the Marcus equation, $\Delta G^{\neq} = (\lambda + \Delta_r G)^2/4\lambda$, where λ is the total reorganization energy.[31] Thus, the reaction of the azide ion with diester **1 a** can be characterized by a slightly positive $\Delta_r G$ value, as exemplified by the results described above. In contrast, the $\Delta_r G$ value for ring opening of **1 aa** is negative because the anion of the α-nitroester is more stable than that of **2 a** (pK_a values for methyl nitroacetate and dimethyl malonate in DMSO are 9.1 and 15.9[32]). Moreover, according to DFT calculations, $\Delta_r G$ for **1 aa** and **1 a** are −5.1 and +5.4 kcal mol^{-1}, respectively.

The lowest energy barriers were calculated for nucleophilic ring opening of cyclopropanes **1 af** and **1 ab** (Table 5, entries 12 and 13; $\Delta G^{\neq} = 20.8$ and 17.7 kcal mol^{-1}, respectively). This result complies with the very high reactivities of **1 ab** and **1 af**, which react with the azide ion at room temperature. These low energy barriers cannot be explained only by the aforementioned dependence on the reaction energy, because the anions of **2 ab** and **2 af** are more stable than that of **2 a** but less stable than that of **2 aa**. Indeed, the pK_a value for malonodinitrile in DMSO is 11.0[33] and the calculated $\Delta_r G$ value is −3.0 kcal mol^{-1}. The obtained results are in line with the higher reactivity of benzylidene derivatives of malonodinitrile and 1,3-indandione towards nucleophiles in comparison with β-nitrostyrene or benzylideneacetylacetone.[34a] This reactivity for Michael acceptors was explained in the terms of "the principle of nonperfect synchronization"[34] according to which the stabilization of the formed carbanion (e.g., through negative charge delocalization or solvent reorganization) is delayed with respect to the progress of the reaction. Another explanation can be given using "total reorganization energy" as defined in the Marcus equation. The stabilization of the nitronate anion is achieved by significant changes in substrate geometry or solvation, for example. However, it means that significant reorganization is also required for the TS in the reaction of **1 aa**. As a result, energy of stabilization of the incipient carbanion in this TS is lower than the reorganization energy required to provide this stabilization; that is, the λ value for the reaction of **1 aa** is sufficiently large. In contrast, the rod-like shape of nitrile groups and the rigid framework of the indanedione moiety provide relatively small values of reorganization energy in the TS for **1 ab** and **1 af**, ensuring their high reactivities.

The variation of donor substituents also affects the reaction barrier. In general, cyclopropane-1,1-diesters with more electron-abundant aromatic substituents demonstrate higher reactivity. For example, 3-indolyl- and 2-pyrrolyl-substituted cyclopropanes **1 v** and **1 p** have lower $\Delta G^{\neq}$ values than **1 a** (by 2.5–3.0 kcal mol^{-1}) and undergo ring opening with the azide ion at lower temperatures (50 and 70 °C, respectively, vs. 100 °C for **1 a**). At the same time, introduction of various substituents into the phenyl group of **1 a** has a relatively small effect on the reactivity of D–A cyclopropanes.

It is noteworthy that 2-unsubstituted cyclopropane-1,1-diester **1 ai** is less reactive than 2-phenyl derivative **1 a**. The introduction of the phenyl group (**1 a** vs. **1 ai**) leads to an increase in cyclopropane reactivity against nucleophilic agents. The same effect is well-known for S_N2 reactions of alicyclic

compounds (e.g., manifesting itself in higher reactivities of benzyl halides in comparison with the corresponding methyl halides).[23] This was ascribed to conjugation in the TS between the three-atom four-electron HOMO, formed by the nucleophile, the central carbon atom and the leaving group, and the π^* orbital of the aryl group. In the studied S_N2-like reactions, the phenyl group is located in a similar position, stabilizing the TS for azide ion attack on the C2 atom of **1a** (Figure 1a).

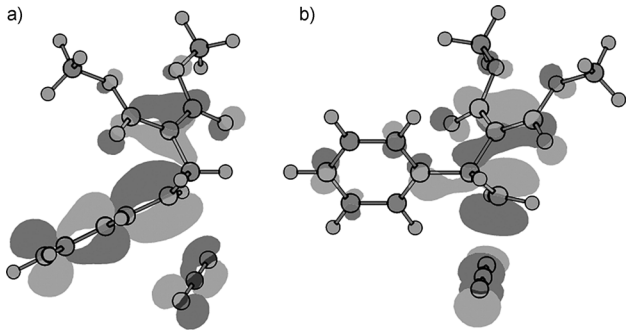


Figure 1. LUMO isosurfaces of S_N2-like transition states for **1a** ring opening with the azide ion: a) C2-attack; b) C3-attack (contour value = 0.04).

A similar effect can also be expected for 2,2-diphenylcyclopropane-1,1-diester **1ag**. However, the optimization of TS for the S_N2-like ring opening of **1ag** with the azide ion showed that the $\Delta G^{\neq}$ value is 31.2 kcal mol^{-1}; that is, 6.8 kcal mol^{-1} higher than the $\Delta G^{\neq}$ value for the reaction of **1a**, and 2.4 kcal mol^{-1} higher than that for the reaction of 2-unsubstituted cyclopropane-1,1-diester **1ai**. Evidently, this result can be explained by steric effects in the reaction of **1ag**; the repulsion between two phenyl groups prevents the efficient conjugation discussed above. Moreover, the steric bulk obstructs the approach of the nucleophile, which clearly manifests itself in a change in the angle (N_3-C2-C1). This angle amounts to 142–148° in the TS for almost all studied D–A cyclopropanes but changes to 131° in the TS for the reaction of **1ag**. Nevertheless, the calculated energy barrier is much lower than that for the reaction of **1ah**, which was found to not react with the azide ion experimentally. Based on the above qualitative agreement between the calculated energy barriers and experimental reactivity (exemplified here as reaction temperature), we proposed that the reaction between **1ag** and the azide ion can be performed at higher temperatures. Indeed, we found that heating of the reaction mixture at 135 °C provided full conversion of **1ag**.

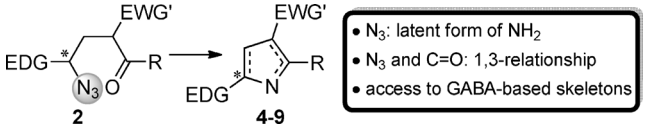
The comparison of energy barriers for **1ag** and **1ai** allowed us to suppose that nucleophilic attack on the C3 atom of **1ag** could compete with attack on the C2 atom. However, our calculations showed that the $\Delta G^{\neq}$ value for the regioisomeric attack is much higher (38.1 kcal mol^{-1}). This is consistent with the experimental data because tertiary azide **3i** was obtained in this reaction. In other words, the aryl group in position 2 of the cyclopropane ring significantly deactivates the vicinal position to attacks by nucleophiles. This conclusion was supported by a higher $\Delta G^{\neq}$ value (31.0 kcal mol^{-1}) for azide attack onto the C3 atom of **1a** in comparison with the energy barriers for azide attack onto the C2 atom (by 6.6 kcal mol^{-1}) as well as the reaction of azide with **1ai** (by 2.2 kcal mol^{-1}). In the corresponding TS, the phenyl group does not demonstrate any stabilizing effect but provides steric hindrance, which decelerates nucleophilic ring opening (Figure 1b). To conclude, our DFT calculations clearly support the proposed S_N2 mechanism for D–A cyclopropane ring opening by the azide ion under the studied conditions. Moreover, we demonstrate that such calculations have the potential to predict the temperatures required to perform ring opening with other D–A cyclopropanes and/or nucleophiles.

Transformations of azides 2

The synthesized azides **2** possess multiple FGs with specific sets of reactivity and, thus, can be easily involved in reactions with both external and internal partners. We demonstrated here that azides **2** can serve as templates for the rapid assembly of complex and diverse nitrogen-containing skeletons often employed in drug design. Modification of azides **2** with suitable agents bearing additional FGs significantly extends the scope of their transformations into a diverse array of five-, six-, and seven-membered N-heterocycles through FG pairing, which includes well-known processes such as aza-Wittig reaction[35] and click [3+2] cycloaddition,[36] as well as original domino reactions.

Synthesis of five-membered N-heterocycles through Staudinger and aza-Wittig reactions

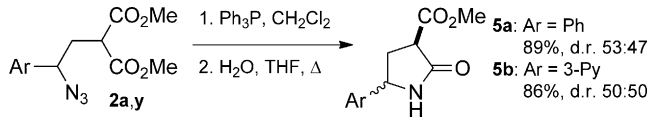
Azide **2** cyclization based on a combination of the azide group as a latent amine function with a γ-placed carbonyl group opens an efficient route to five-membered N-heterocycles, especially various GABA-based skeletons. In this part of the current work, we used synthetic pathways involving Staudinger/aza-Wittig reactions that led to pyrrolidone and pyrroline derivatives, which can be further transformed into polyfunctionalized pyrroles (Scheme 5).



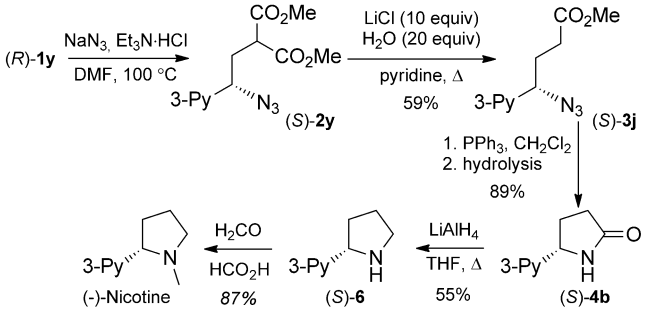
Scheme 5. Use of azides **2** as a latent amine in the synthesis of five-membered N-heterocycles.

Thus, the reduction of azides **2a** and **2y** through Staudinger reaction/iminophosphorane hydrolysis produces aminomalonates, which undergo spontaneous 1,5-cyclization furnishing γ-lactams **5a** and **5b** in high yields (Scheme 6).

The present methodology provides an easy and efficient access to natural products, for example the tobacco alkaloid family. On the basis of this reductive cyclization, we developed a total synthesis of (*S*)-nicotine starting from optically active 3-



Scheme 6. Synthesis of γ-lactams through reductive cyclization of **2**.

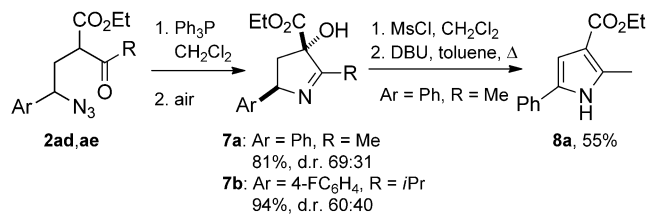


Scheme 7. Total synthesis of (−)-nicotine.

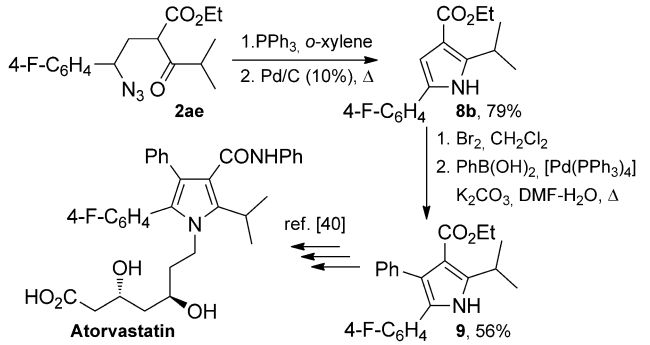
pyridyl-derived cyclopropane (*R*)-**1y** (Scheme 7). It is noteworthy that Krapcho dealkoxycarbonylation of (*S*)-**2y** was carried out in pyridine as a solvent to prevent the alkylation of the 3-pyridyl moiety in product **3j** with CH_3Cl evolving during dealkoxycarbonylation. Treatment of (*S*)-**3j** with Ph_3P produced lactam (*S*)-**4b**. Its reduction with $LiAlH_4$ followed by reductive methylation of the resulting pyrrolidine (*S*)-**6** finalized the synthesis of (−)-nicotine. This synthesis provides a rapid enantioselective access not only to nicotine (which attracts much attention due to its effects on the central nervous system as well as its use as an insecticide) but also to its metabolites, which exhibit various types of bioactivity.[37]

The introduction of ketoazides into a reaction with phosphane provides rapid access to densely substituted pyrrolines and pyrroles. Thus, the treatment of ketoazides **2ad** and **2ae** with Ph_3P induced a domino process consisting of Staudinger and aza-Wittig reactions as well as oxidation by air[38] leading to 3-hydroxy-4,5-dihydro-3*H*-pyrroles **7a** and **7b** (Scheme 8). The structure of **7a** was unambiguously proved by single-crystal X-ray analysis.[39] The aromatization of **7a** afforded pyrrole derivative **8a**.

To display the utility of this novel route to pyrroles, we applied it in the synthesis of the pyrrole subunit **9** of atorvastatin (Scheme 9), the calcium salt of which is known as cholesterol-lowering medication Lipitor. Synthesis of **9** was initiated by a Staudinger/aza-Wittig reaction of **2ae** followed by dehydro-



Scheme 8. Synthesis of pyrrolines **7** and pyrrole **8** from **2**.



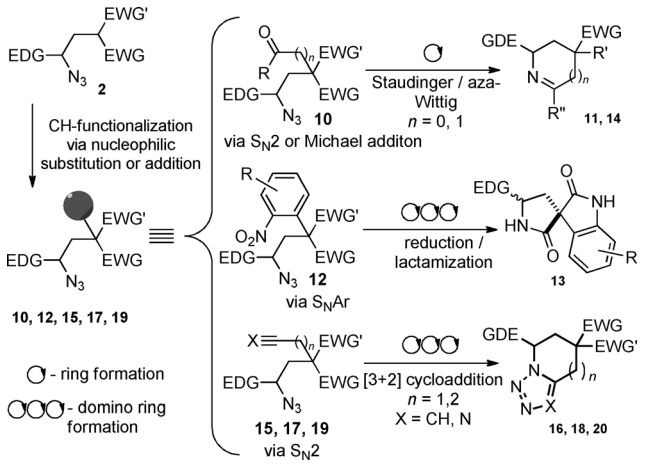
Scheme 9. Formal total synthesis of atorvastatin.

genation, yielding trisubstituted pyrrole **8b**. The bromination of **8b** and further Suzuki cross-coupling afforded tetrasubstituted pyrrole **9**, the transformation of which into atorvastatin was reported earlier.[40]

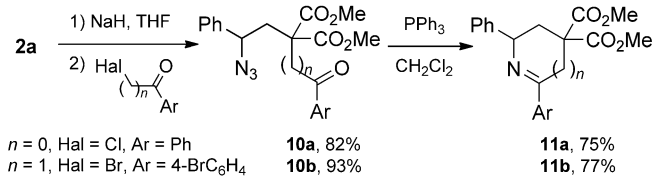
Synthesis of N-heterocycles through functionalization of activated CH group as the key step

The presence of an activated methine group in **2** allows for branching and additional functionalization of their alkyl chain through nucleophilic substitution or addition reactions. These simple operations furnish wide opportunities to synthesize a great variety of highly functionalized acyclic and N-heterocyclic compounds. In the present work, we extended the synthetic utility of azides **2** considerably through their alkylation (S_N2 or Michael addition), acylation and arylation (S_NAr) allowing for further intramolecular construction of heterocyclic systems with various ring sizes (Scheme 10).

The synthesis of pyrroline **11a** can exemplify the employment of C–H functionalization in **2** through nucleophilic substitution for the purpose of five-membered ring assembly (Scheme 11). We acylated azide **2a** with benzoyl chloride and then treated the product **10a** with Ph_3P to initiate a sequence



Scheme 10. Different modes of azide **2** cyclization after activated CH functionalization.

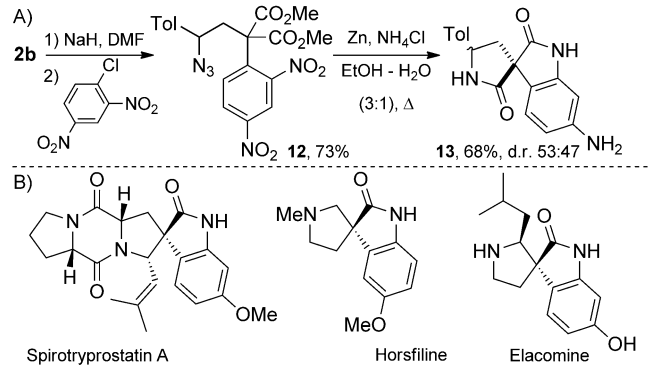


Scheme 11. Synthesis of 1-pyrrolines and 1-piperideines from azides **2** through an S_N/Staudinger/aza-Wittig reaction sequence.

of Staudinger/aza-Wittig reactions leading to **11a** in a high yield.

The introduction of a two-carbon linker through alkylation of azides **2** with α-haloketones opens a simple way to construct six-membered rings. Thus, starting from azide **2a**, we obtained tetrahydropyridine **11b** by the alkylation of **2a** with 4-bromophenacyl bromide followed by Staudinger/aza-Wittig reactions (Scheme 11).

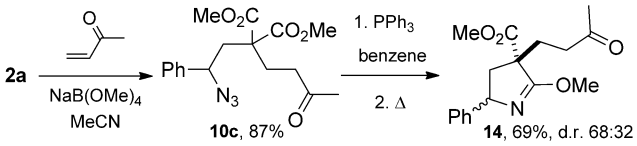
Functionalization of azides **2** through arylation provides opportunities for the synthesis of benzannulated systems. Thus, we developed an extremely simple approach to spirooxindole-3,3′-pyrrolidine **13** (Scheme 12A), the scaffold of which



Scheme 12. Synthesis of spirooxindole-3,3′-pyrrolidine **13** from azide **2b** through S_NAr/reduction/γ-lactamization (A) and selected examples of spirooxindole alkaloids (B).

is present in numerous spirooxindole alkaloids, such as spirotryprostatins A and B, pteropodine, elacomine, and horsfiline (Scheme 12B).[41] Our approach consists of preliminary arylation of azide **2b** with chloro-2,4-dinitrobenzene through an S_NAr reaction giving **12** followed by the transformation of **12** into **13**. The latter reaction can be viewed as a tandem of double domino sequences involving simultaneous N_3 and NO_2 reduction[42] that initiates double γ-lactamization leading to spirooxindole **13**. This unique process, in which three functional groups of the parent azides **2** are involved at once, differs from many other approaches to spirooxindole-3,3′-pyrrolidine by affording simultaneous construction of indole and pyrrolidine cores. In terms of bioactivities, spirooxindole-3,3′-pyrrolidin-2-one derivatives were shown to be efficient antagonists of the CRTH2 (DP2) receptor, with the corresponding K_i values at the nanomolar level.[43] They also demonstrate moderate cytotoxicity against selected cancer cells.[44] Moreover, the ability of the pyrrolidone moiety to undergo selective reduction[45] as well as the tendency of the NH_2 group to undergo easy substitution by H or various functional groups through diazonium salt formation enables compound **13** to be transformed into more complex structures of biological relevance.[46]

Nucleophilic addition of the Michael type was also found to be suitable for the alkylation of azides **2** and, thus, for the synthesis of branched polyfunctional compounds **10** with a 1,5-relationship between the azide and carbonyl functions ($n=2$) (Scheme 10). Thus, ketoazide **10c** was synthesized by Michael addition of **2a** to methyl vinyl ketone (Scheme 13). For



Scheme 13. Azide **2** functionalization through Michael addition and further Staudinger/aza-Wittig reaction.

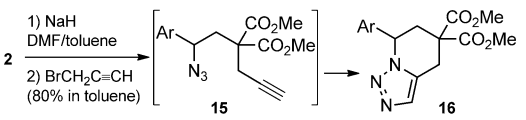
compounds of type **10**, and **10c** in particular, Staudinger/intramolecular aza-Wittig reactions can proceed through two alternative pathways: namely, through nucleophilic attack of intermediate iminophosphoranes on the electrophilic site of keto- or ester groups, which, in the case of **10c**, lead to seven- or five-membered rings, respectively. We found that, despite higher electrophilicity of the keto-group, chemoselective 1,5-cyclization through the ester group takes place for **10c** under Staudinger/aza-Wittig reaction conditions (Scheme 13). As a result, pyrroline **14** was obtained in good yield. To our knowledge, this process is the first example of ester function priority over a keto-group in reactions with aza-nucleophiles, when cyclizations with both ester and keto group could produce normal rings having no steric repulsions.

Synthesis of triazolo- and tetrazolopyridines through a sequence of activated CH-group functionalization and [3+2] cycloaddition

[3+2] Cycloadditions to double or triple bonds are the principal transformations of azides among those that proceed without N_2 elimination. In this group of transformations, azide–alkyne cycloaddition is of special importance. We elaborated a simple access to triazolo- and tetrazolopyridines and -azepines through intramolecular [3+2] cycloaddition of the N_3 moiety to the C≡C and C≡N bonds, which were preinstalled by means of C–H functionalization of azides **2** (Scheme 10).

Surprisingly, introduction of the propargyl moiety to azides **2** through their alkylation with propargyl bromide initiates spontaneous Huisgen azide–alkyne [3+2] cycloaddition leading to triazolopyridines **16** in good yields (Table 6). A slight decrease in yield was observed in reactions of azides **2u** and **2y**, which can be prone to side-processes due to the presence of reactive heteroaryl substituents.

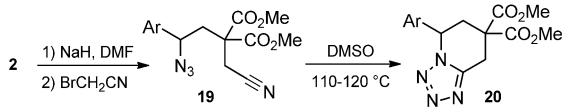
Table 6. Synthesis of triazoles **16** through domino propargylation of azides **2** and [3+2] cycloaddition.[a]



2	Ar	15,16	*t* [h]	Yield of **16** [%][b]
a	Ph	**a**	1.5	78
b	4-MeC_6H_4	**b**	1.5	69
f	4-$MeOC_6H_4$	**c**	1.5	71
k	3,4,5-$(MeO)_3C_6H_2$	**d**	1.5	68
o	4-NCC_6H_4	**e**	2	72
y	3-Py	**f**	1.5	53
u	4-(1-Me)Ind	**g**	1.5	52

[a] Reaction conditions: 0.5 M solution of **2** in DMF/toluene (1:1), NaH (1.2 equiv), propargyl bromide (1.5 equiv). [b] Yield of isolated product.

Table 7. Synthesis of tetrazolopyridines **20**.[a]

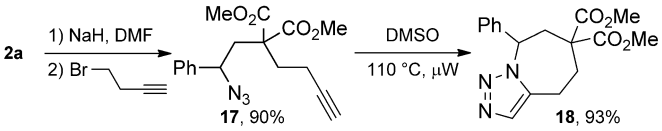


2	Ar	*t* [h]	19, 20	Yield of **19** [%][b]	*t* [h]	Yield of **20** [%][b]
a	Ph	12	**a**	85	25	92
h	2-BnO-3-$MeOC_6H_3$	15	**b**	67	20	83
k	3,4,5-$(MeO)_3C_6H_2$	14	**c**	69	22	71
q′[c]	2-Fu	15	**d**	77	30	74
r	2-Th	15	**e**	75	23	72
t	2-benzothienyl	19	**f**	79	34	68
u	4-(1-Me)Ind	26	**g**	84	40	68

[a] Reaction conditions: 0.5 M solution of **2** in DMF, NaH (1.1 equiv), 2-bromoacetonitrile (1.2 equiv). [b] Yield of isolated product. [c] Diethyl ester **2q′** was used as a starting material.

The unique character of this domino process reveals itself in the extreme ease of the intramolecular azide–alkyne cycloadditions (AAC), which proceed spontaneously under very mild, catalyst-free conditions. Presumably, this is caused by the proximity of reacting fragments[47] in intermediates **15** and the formation of a stable bicyclo[4.3.0]nonane system in the resulting structures **16**.

In contrast, reaction of azide **2a** with homopropargyl bromide produces **17** as a stable product of alkylation, which does not undergo spontaneous azide–alkyne cycloaddition under ambient conditions (Scheme 14). The transformation of



Scheme 14. Synthesis of triazoloazepine **18**.

17 into triazoloazepine **18** through intramolecular azide–alkyne [3+2] cycloaddition proceeds only under prolonged heating at 110 °C in a microwave reactor. In contrast to aza-Wittig reaction-derived cyclization, which fails to give a seven-membered ring (Scheme 13), azide–alkyne [3+2] cycloaddition proved to be less sensitive to the ring-size effect and produces challenging seven-membered rings albeit at higher temperature.

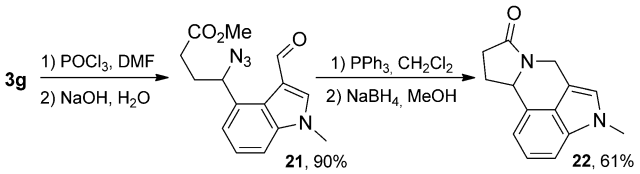
Analogously, alkylation of azides **2** with bromoacetonitrile affords stable acyclic products **19**, which undergo azide-nitrile [3+2] cycloaddition to furnish tetrazolopyridines **20** only under prolonged heating at 110–120 °C (Table 7).

In general, this methodology including D–A cyclopropane ring opening with azide ion, alkylation of product with a triple bond containing halide compound followed by [3+2] cycloaddition provides a simple efficient route to aryl-substituted triazolo[1,5-*a*]pyridines and -azepines as well as tetrazolo-[1,5-*a*]pyridines, which are very attractive as potent pharmacological agents[48] that are difficult to access by other methods.

Our preliminary experiments in vitro on HEK293T, MCF7, and SiHa cell lines did not reveal any cytotoxicity of synthesized triazoles **16** and tetrazoles **20** up to concentrations of 1 mM. These results open opportunities to use these compounds in screening for other types of bioactivity.

Synthesis of N-heterocycles through EDG functionalization

The presence of (hetero)aryl or alkenyl substituents in azides **2** and **3** opens up a broad range of possibilities for their further functionalization through S_EAr, cross-coupling, oxidation, and other reactions. As an example of such functionalization, we transformed indole-derived azide **3g** into dipyrrolo[2,1-*a*:4′,3′,2′-*de*]isoquinoline **22** through formylation of the indole ring, producing azidoaldehyde **21**, followed by the Staudinger/aza-Wittig/reductive cyclization sequence (Scheme 15).



Scheme 15. Synthesis of tetracycle **22** from azide **21** through EDG functionalization.

This is the first preparative approach to the dipyrrolo[2,1-*a*:4′,3′,2′-*de*]isoquinoline scaffold.[49] Such a scaffold should be of interest for medicinal chemistry because pyrrolo[4,3,2-*de*]isoquinolines, the closest polycyclic systems, have demonstrated a broad range of bioactivities.[50]

Conclusion

We have developed a valuable new method that involves ring opening of D–A cyclopropanes with the azide ion, providing

straightforward access to libraries of polyfunctional azides of broad structural diversity. Exceptional regioselectivity and stereospecificity of the ring opening is furnished by the S_N2-like mechanism of this reaction. This conclusion was supported by DFT calculations, which show that the optimized transition states correspond to the S_N2-like reaction, whereas nucleophilic attack on the unsubstituted C3 atom has a significantly higher energy barrier than that for the donor-substituted C2 atom.

The obtained azides were shown to be essential building blocks for the assembly of a broad skeletal array of five-, six-, and seven-membered N-heterocyclic systems of biological relevance. Simple synthetic sequences based on the elaboration of azides into more complex structures involve their modification or additional functionalization followed by a variety of ring-forming processes. We have described modular synthetic pathways incorporating aza-Wittig, lactamization, and 1,3-dipolar cycloaddition reactions as ring-forming processes and yielding multisubstituted pyrrolidones, pyrrolines, pyrroles, 1-piperideines, spirooxindole-3,3′-pyrrolidines, triazolo[1,5-*a*]pyridines and -azepines, tetrazolo[1,5-*a*]pyridines, and dipyrrolo[2,1-*a*:4′,3′,2′-*de*]isoquinolines. The present methodology was also exploited in the synthesis of natural products and synthetic drugs, namely (−)-nicotine and atorvastatin (Lipitor). The impressive synthetic potential of synthesized azides is not restricted to this set of transformations and reaches beyond the present work, allowing for the employment of manifold functionalities of these compounds and for further design of synthetic sequences for combinatorial, diversity- or biology-oriented synthesis in drug discovery efforts.

Experimental Section

General procedure for the synthesis of azides 2: **Caution!** Although we did not experience any problems with the studied reactions, a small amount of toxic and potentially explosive HN_3 can be formed during these processes. Safety precautions are required. To a solution of cyclopropane **1** (0.5 M) in anhydrous DMF, triethylamine hydrochloride (2 equiv) and sodium azide (2 equiv) were added in a single portion under an argon atmosphere. The resulting mixture was stirred under the specified conditions, poured into H_2O (10 mL), and extracted with ethyl acetate (3×15 mL). The combined organic fractions were washed with water (5×10 mL) and dried with Na_2SO_4. The solvent was evaporated and the product was purified by column chromatography on silica gel.

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Keywords: azides · donor–acceptor systems · heterocycles · nitrogen heterocycles · nucleophilic substitution

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FULL PAPER

Nitrogen Heterocycles

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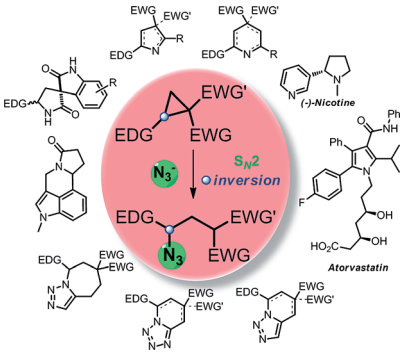
■■ – ■■

Ring Opening of Donor–Acceptor Cyclopropanes with the Azide Ion: A Tool for Construction of N-Heterocycles



A new world of opportunities: Stereospecific ring opening of donor–acceptor cyclopropanes with the azide ion gives rise to densely functionalized building blocks that are valuable for the assembly of a diverse range of N-heterocycles (see scheme). These synthetic opportunities are provided by the simultaneous presence of the N_3 group, which reacts as a latent amine or 1,3-dipole, easily modifiable donor and acceptor substituents, as well as the activated CH fragment.

A kaleidoscope of synthetic opportunities…
…is provided by a new family of densely functionalized organic building blocks produced by means of one simple operation; regioselective and stereospecific ring opening of donor–acceptor cyclopropanes with the azide ion. The tolerance of functionalities versus their strategic placement combined with ability to undergo selective modification allow these building blocks to easily yield a great diversity of *N*-heterocycles of synthetic and biological relevance. For more details, see the Full Paper by E. M. Budynina, I. V. Trushkov et al. on page ■■ ff.