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Unexpected Heterocyclic Products from Cycloaddition Reactions of Nonsymmetrical Allenyl Aldoketazines with Substituted Alkynes

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Dedicated to Professor Dr. František Liška on the occasion of his 70th birthday

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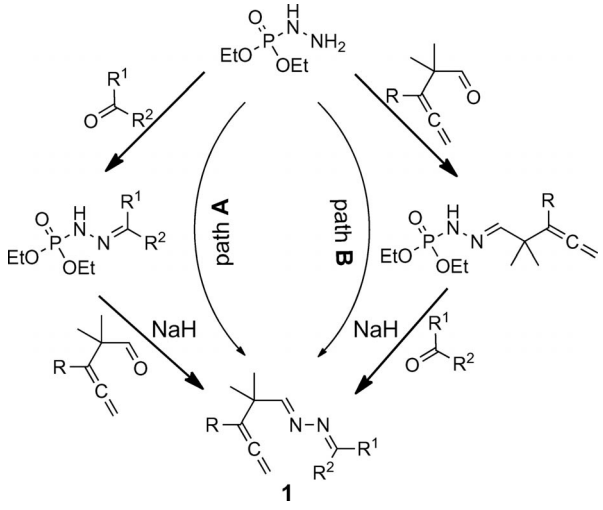
Thermally initiated cycloaddition reactions of nonsymmetrical allenyl azines **1** with alkynes or other dipolarophiles usually lead to compounds with three fused, five-membered heterocyclic rings. With alkynes with pronounced "push–pull" systems, however, the reaction ends with the formation of substituted pyrrolidino[1,2-*b*]pyrazoles **4** and, in the case of azines with trifluoromethyl substitution, ring opening leads to the isolation of compounds **9**. Reaction mechanisms for these transformations are proposed. The molecular structures of the new heterocycles **4** and **9** were confirmed by X-ray crystal structure analysis.

Introduction

Allenyl derivatives are nowadays often explored in organic synthesis, and the syntheses of numerous organic compounds with biological activity have been based on the allenyl synthon.[1] In our laboratories, we have been interested in the synthesis of nonsymmetrical allenyl azines **1** and their transformations.[2] The requisite starting 3-alkyl-2,2-dimethylpenta-3,4-dienals were prepared by Claisen–Cope rearrangement[3] of (3-alkylprop-2-ynyl) (2-methylpropenyl) ethers and their azines **1** by Zwierzak's method[4] (Scheme 1).

We found that compounds **1** are capable of undergoing thermally initiated combined intra-intermolecular criss-cross cycloaddition with dipolarophiles.[2a] Although the classic "criss-cross" reactions have been known for almost a hundred years,[5] our combined intra-intermolecular approach is rather new.[2] Generally, criss-cross cycloadditions proceed as two consecutive 1,3-dipolar cycloaddition reactions of heterodienes, most often azines, with dipolarophiles[6] and may be classified as a special type of [3+2] cycloaddition or 1,3-dipolar cycloaddition.[7] This fact was proven in 1973 when a stable 1,3-dipole was identified by X-ray structure analysis.[8]



Scheme 1. Two pathways using Zwierzak's protection for the preparation of nonsymmetrical azines **1**.

Nonsymmetrical allenyl azines **1**, when used as starting compounds, react with various dipolarophiles to generate products that are either tricyclic heterocycles **2** or, in the case of thermal stress without any dipolarophile, fused bicyclic products **3** (Scheme 2).

To the best of our knowledge, no simple intermolecular criss-cross cycloadditions[5] in which two molecules of a dipolarophile react with one molecule of azine **1** have hitherto been observed.

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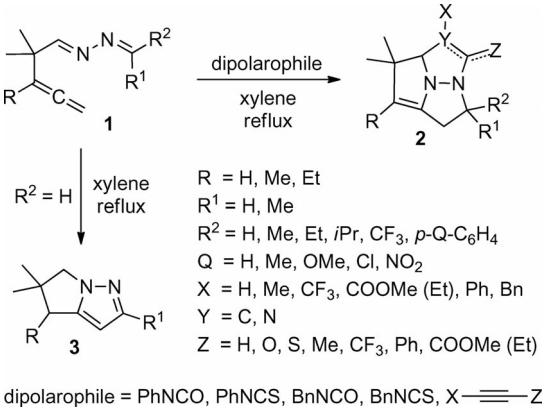


Scheme 2. Overview of transformation products of allenyl azines **1**.

Results and Discussion

In this paper, we demonstrate the reactivity of allenyl aldoketazines **1** (Table 1) with variously substituted alkynes **A**–**F** (Table 2) in anhydrous boiling xylene and propose mechanisms to explain the product formation. Although the usually obtained products are heterocycles of type **2**, with three fused five-membered rings, we observed the formation of new fused bicyclic heterocyclic products **4** and **9** (Scheme 3). The products were isolated and identified.

Table 1. Nonsymmetrical allenyl aldoketazines **1a**–**d** with their yields (%).

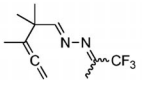
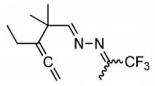
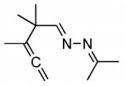
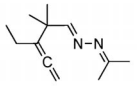
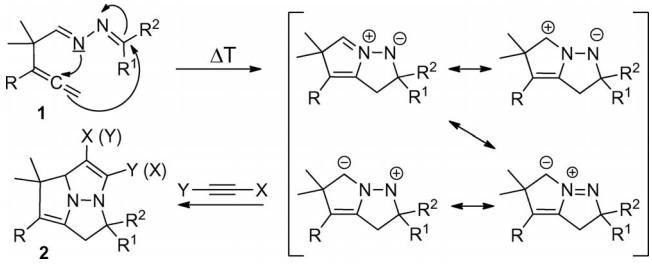
			
1a (92%)	**1b** (67%)	**1c** (73%)	**1d** (80%)

Table 2. Six selected alkynes **A**–**F** for criss-cross cycloaddition.

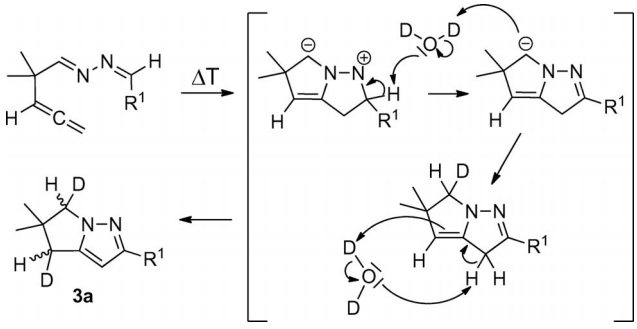
MeOOC—≡—COOMe	**A**
F_3C—≡—COOMe	**B**
≡—COOMe (Et)	**C**
Ph—≡	**D**
≡—COOEt	**E**
Ph—≡—COOEt	**F**

We assume that the intermediate in the transformation is the bicyclic 1,3-dipole formed in anhydrous boiling xylene by intramolecular attack on the central carbon atom of the allenyl group by a nitrogen atom of the azine moiety (Scheme 4). Such a 1,3-dipole, also predicted by quantum chemical calculations,[9] then reacts with the relevant dipolarophile in a combined intra-intermolecular criss-cross cycloaddition to form products of type **2** with three fused five-membered rings.



Scheme 4. Formation of combined intra-intermolecular criss-cross cycloaddition products **2**.

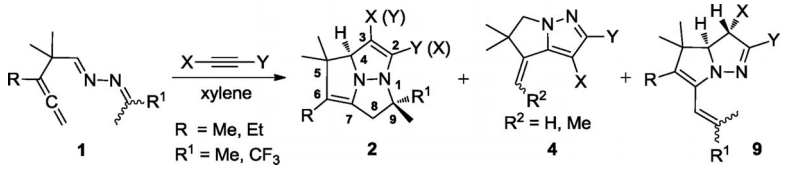
The formation of bicyclic pyrrolidino[1,2-*b*]pyrazoles **3** (Scheme 2) in cases where no dipolarophile is present, or where a poorly reactive dipolarophile is used, depends on the presence of at least one proton on the azine moiety. Otherwise, only tar-like products are recovered. Compound **3** then forms as a product of ensuing proton shifts in the primarily formed 1,3-dipole. The process probably proceeds with the assistance of a catalytic amount of water. This assumption was proven by performing the reaction in the presence of D_2O (Scheme 5).



Scheme 5. Mechanism of the formation of pyrrolidino[1,2-*b*]pyrazoles **3** in the presence of D_2O.

Pyrrolidino[1,2-*b*]pyrazoles are known to be biologically active structures. In the traditional Indian system of medicine, the extract from *Withania somnifera* Dun. is commonly known as "Indian Ginseng".[10–12]

Our experiments were carried out with the selected allenyl aldoketazines **1a**–**d** (Table 1) and six different alkynes **A**–**F** (Table 2). Because aldoketazines without a proton on one side of the azine moiety were used, the formation of bicyclic products **3** were excluded, and this simplified the



Scheme 3. Three possible heterocyclic products by cycloaddition of **1** with alkynes.

identification of the products after the reaction. We therefore expected typical criss-cross products **2** to be obtained.[2]

The reactions of aldoketazines **1a** and **1b**, both of which bear CF_3 groups, were monitored by TLC and ^{19}F NMR spectroscopy and were stopped at about 80% conversion (16.5 h). Extending the reaction time further led only to a negligible increase in conversion along with the formation of decomposition products. Monitoring the reactions of aldoketazines **1c** and **1d** was significantly more difficult and each reaction had to be repeated several times; reaction times were in the range 6–24 h, leading to conversions of 60–100% (determined by ^1H NMR spectroscopic analysis).

When the symmetrical alkyne **A** (Table 2) was treated with azines **1a**–**d** (Table 1), only one stereoisomer was formed (Table 3, entry 1). Phenylacetylene **D** also afforded only one stereoisomer (Table 3, entry 6) and the second possible isomer was never observed. Conversely, the reactions of alkynes **B** and **C** with the same azines **1a**–**d** yielded both possible regioisomers of products **2** (Table 3, entries 2 and 3, or entries 4 and 5, respectively). The results show that the regioselectivity is markedly higher when non-fluorinated azines (**1c** and **1d**) are used, which implies that after the intramolecular step, the activation of the formed 1,3-dipole by the CF_3 group is considerably higher and alkyne attack is equally likely to occur at both possible sites. Alkynes **E** and **F**, both of which have pronounced "push–pull" systems, represent exceptions in cycloaddition; they either did not afford products **2** at all in some cases (Table 3, entries 7, 8, 10, and 11), or gave low yields (Table 3, entry 7). Instead, unexpectedly, either products **4** containing an exocyclic double bond were exclusively observed (Table 3, entries 9 and 12) or products **9** with an open ring were isolated (Table 3, entry 13).

Table 3. Products of reactions of azines **1a**–**d** with alkynes **A**–**F** and their yields.[a]

Entry	Alkyne	Products of reactions of azines **1** (%)			
		a	**b**	**c**	**d**
1	**A**	**2Aa** (74)	**2Ab** (67)	**2Ac** (63)	**2Ad** (71)
2	**B**	**2Ba$_1$** (28)	**2Bb$_1$** (21)	**2Bc$_1$** (15)	**2Bd$_1$** (19)
3		**2Ba$_2$** (36)	**2Bb$_2$** (25)	**2Bc$_2$** (58)	**2Bd$_2$** (51)
4	**C**	**2Ca$_1$** (37)	**2Cb$_1$** (35)	**2Cc$_1$** (22)	**2Cd$_1$** (19)
5		**2Ca$_2$** (31)	**2Cb$_2$** (30)	**2Cc$_2$** (47)	**2Cd$_2$** (56)
6	**D**	**2Da** (51)	**2Db** (47)	**2Dc** (36)	**2Dd** (32)
7	**E**	**2Ea$_1$** (7)	–[b]	**2Ec$_1$** (ca. 5)	–[b]
8		**2Ea$_2$** (31)	**2Eb$_2$** (16)	**2Ec$_2$** (41)	–[b]
9		**4a** (27)	**4b** (34)	**4a** (34)	**4b** (37)
10	**F**	–[b]	–[b]	–[b]	–[b]
11		–[b]	**2Fb$_2$** (20)	–[b]	–[b]
12		**4c** (17)	**4d** (34)	**4c** (30)	**4d** (39)
13		**9a** (55)	**9b** (17)	**9c** (traces)	–[b]

[a] n_1 and n_2 denote regioisomers 1 and 2, respectively, in reaction with nonsymmetrical alkyne. [b] No product observed.

The resulting products **2** were purified by preparative TLC and HPFC. From crystallographic measurements, detailed information about the molecule **2** (Figure 1) was obtained that was consistent with our previous results.[2] Products **2**, which were formed from azines **1a** and **1b**, were isolated only as single diastereoisomers, with the hydrogen atom at the stereogenic center C4 and the CF_3 group at stereogenic center C9 oriented towards the same side of the molecule (Scheme 3, Figure 1).

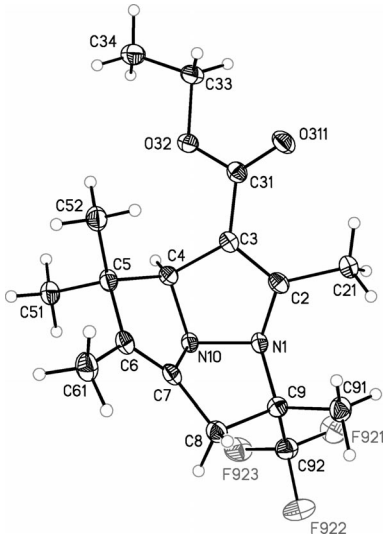


Figure 1. X-ray crystal structure of criss-cross product **2Ea$_2$**.

From NMR spectroscopic measurements it can be concluded that the new product **4** does not contain a stereogenic center because the two methyl groups give rise to only one signal. Furthermore, we concluded that this structure is a cycloadduct containing both the former alkyne and azine parts. This assumption was fully corroborated by X-ray structure analysis (Figure 2). Products **4a**–**d** are new pyrrol-

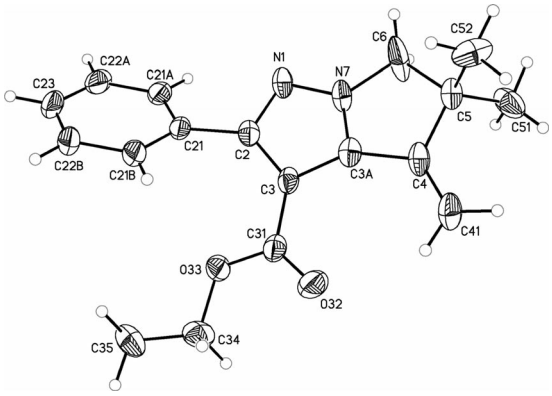
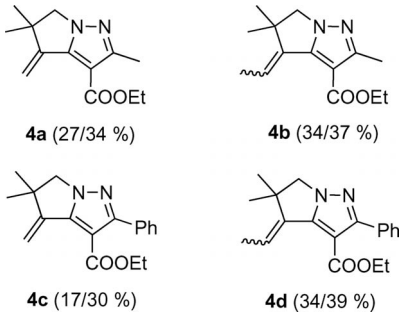


Figure 2. X-ray crystal structure of the unexpected product **4c**.

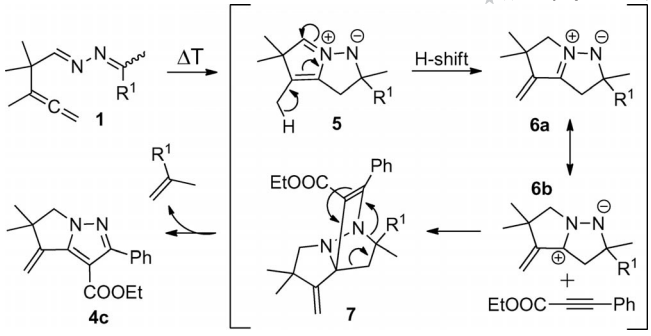


Scheme 6. Pyrrolidino[1,2-*b*]pyrazoles **4a**–**d** with isolated yields.

idino[1,2-*b*]pyrazoles with an exocyclic double bond, and were formed in relatively high yields (Table 3, Scheme 6).

In Scheme 6, the structures of **4a**–**d** are presented with two yields; the first is the yield from the reaction with fluorinated azines **1a** and **1b** and the second is the yield from the non-fluorinated derivatives **1c** and **1d**.

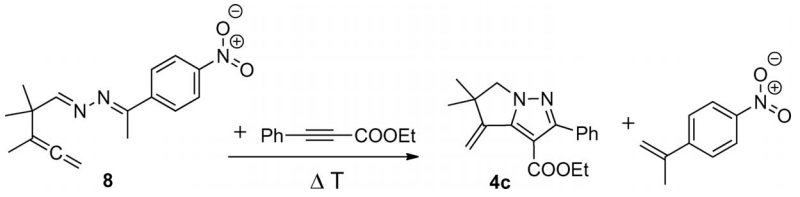
The mechanism of formation of the new bicyclic products **4** may be explained in terms of an intramolecular attack of the nitrogen atom of the azine skeleton on the allenyl group to produce bicyclic 1,3-dipole **5**. However, the intermolecular 1,3-dipolar cycloaddition to the relevant alkyne is preceded by a proton shift and the formation of a new 1,3-dipole **6**. At the end of the transformation, the substituted alkene is cleaved from the formed structure **7** and the final product **4** is formed (Scheme 7). The structure of the leaving alkene corresponds to that of the nonsymmetrical azine ketone part.



Scheme 7. Proposed mechanism for the formation of products **4**.

To confirm the proposed mechanism for the formation of the new heterocycles **4**, we synthesized allenyl azine **8** (Scheme 8), which contains a larger ketone moiety, and tried to capture the leaving alkene after the reaction. Thus, reaction of compound **8**, having a 4-nitroacetophenone moiety bound at the azine, afforded structure **4c** and enabled isolation of 4-(propen-2-yl)nitrobenzene, which supported our proposed mechanistic interpretation.

Another question that arises is why such a process takes place, because it is interesting that in the case of alkyne **F** the new process prevails. Scheme 9 shows a possible mechanistic rationale.



Scheme 8. Support for the proposed mechanism involved in the formation of product **4**.

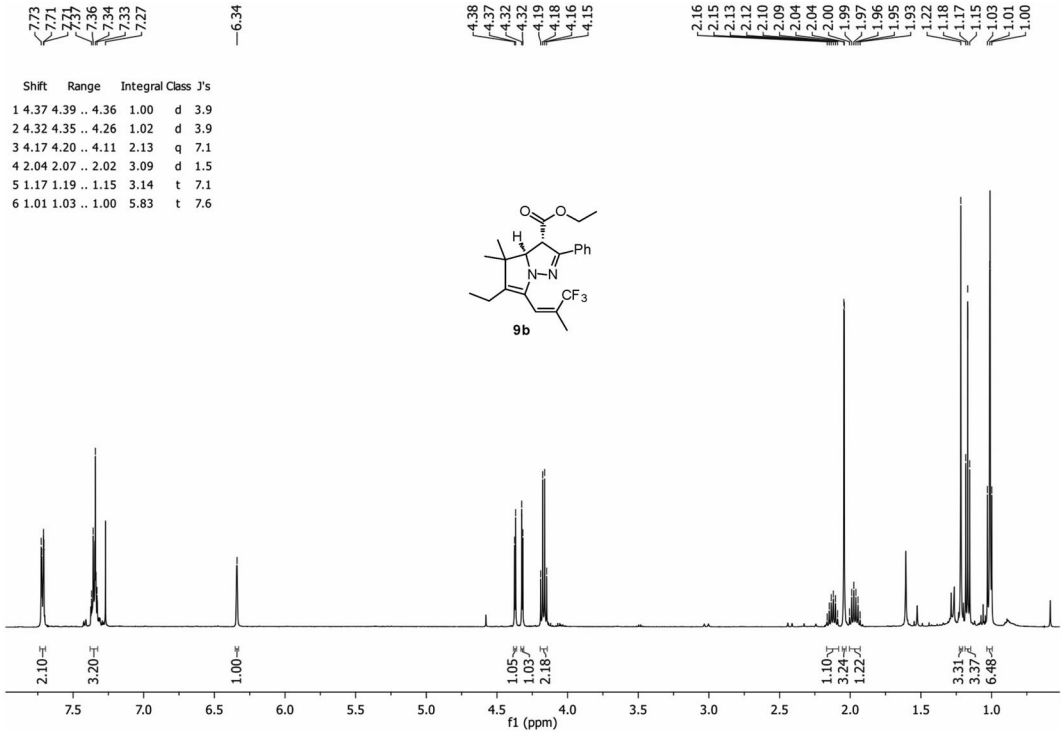
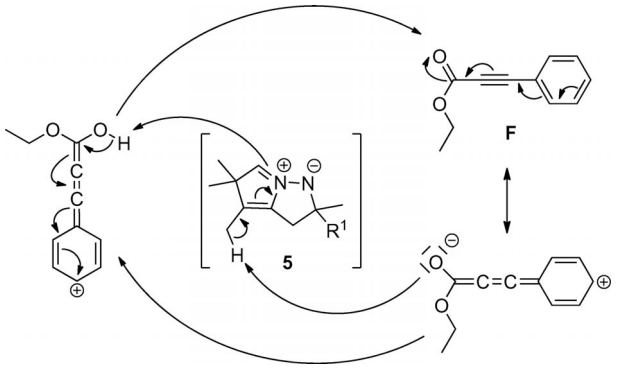


Figure 3. ^{1}H NMR spectrum of the separated unexpected product **9b**.



Scheme 9. Proton transfer mediated by alkyne **F** during the formation of products **4**.

Whereas in alkynes **A**–**C** the electron-withdrawing ester group strongly activates the triple bond and enables reactions leading to the expected criss-cross products **2**, in alkyne **F** the effect of the substitution at the other side of the alkyne moiety probably plays a very important role. The phenyl ring participates in conjugation with the ester group and stabilizes the partial positive charge at the triple bond through resonance. Thus, the reactivity of alkyne **F** in the cycloaddition reaction is decreased while at the same time, the basicity of the oxygen atom of the ester group is increased. This is probably the reason for the unusual reactivity, with the alkyne presumably acting as a proton-transfer agent (Scheme 9).

However, the reactions of alkyne **F** yielded further new compounds of type **9** after purification by preparative TLC (Figure 3). From the ^{1}H NMR spectrum, the presence of an ethoxycarbonyl group and stereogenic centers could be deduced. Finally, we succeeded in preparing a single crystal of **9a** that was suitable for X-ray structure analysis (Figure 4). The crystal structure revealed that the protons at both stereogenic centers were *trans*-orientated and that the configuration at the exocyclic double bond was *E*. The alternative *Z* configuration was only found for the compound with R = Et (**9b**). We must state here that compounds of type **9** were only obtained from reactions of fluorinated azines **1a** and **1b** with alkyne **F**.

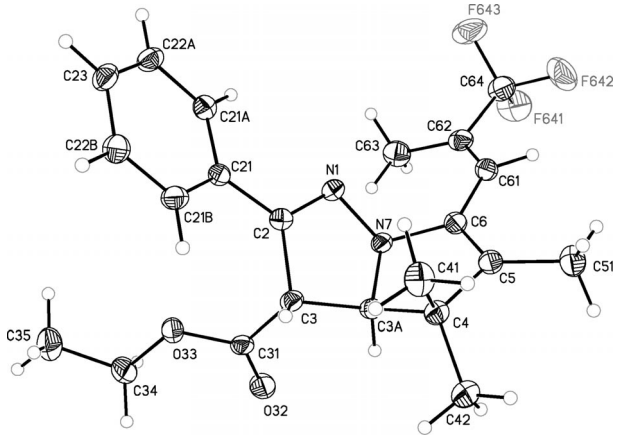
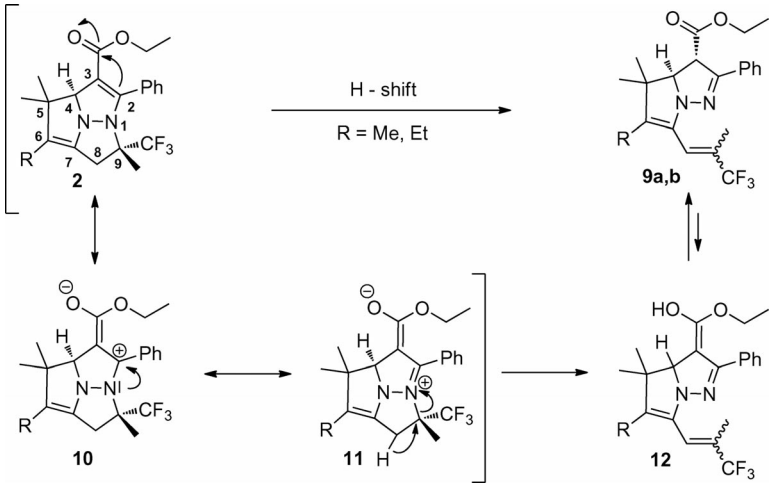


Figure 4. X-ray crystal structure of the unexpected product **9a**.

The structure of **9** indicates that it must be a product derived from tricyclic compound **2** by the cleavage of one single bond (Scheme 10). The double bond between the ester and phenyl groups in the tricyclic product **2** is in conjugation with the carbonyl function, which forms a partial positive charge at C2 in the vicinity of the nitrogen atom (structure **10**). The effect of the electron-withdrawing CF_3 group in leading to further transformation is clearly apparent in its other resonance structure **11**, in which the positive charge is located on the nitrogen atom. The reaction then proceeds by a proton shift, accompanied by splitting of the bond between C9 and N1 leading to intermediate **12**, which is a tautomeric form of compounds **9a**,**b**.

Conclusions

The reactivities of six selected alkynes **A**–**F** with four nonsymmetrical allenyl aldoketazines **1a**–**d** in combined intra-intermolecular criss-cross cycloaddition reactions have been investigated. Whereas the products of such reactions with al-



Scheme 10. Proposed mechanism for the formation of products **9**.

kynes **A**–**D** were compounds of type **2**, new fused bicyclic heterocycles **4** and **9** were formed as the main products of the reactions with alkynes **E** and **F**. These new compounds have been fully characterized by standard spectroscopic analysis, and the structures of some have been established by X-ray crystallography. All of the observed criss-cross cycloadditions were diastereoselective. Reactions of allenyl azines **1a** and **1b**, which bear trifluoromethyl groups, with nonsymmetrical alkynes showed low regioselectivity. The close similarity of the new pyrrolidino[1,2-*b*]pyrazoles to the skeleton of the biologically active alkaloid *withasomnine* suggests a potential for some interesting features. The method represents a straightforward route for the preparation of new nitrogen-containing heterocycles with three fused five-membered rings as well as pyrrolidino[1,2-*b*]pyrazoles.

Experimental Section

Alkynes were purchased from commercial suppliers and were used after purification by distillation. Ethyl 4,4,4-trifluoro-2-butynoate (**B**) was prepared according to a literature method.[13] Petroleum ether (PE) had a boiling range of 40–60 °C. Diethyl ether and benzene were distilled from sodium/benzophenone before use. Xylene (mixture of isomers) was dried and distilled from sodium/benzophenone and stored over dry molecular sieves (4 Å). All reactions were carried out under a dry argon atmosphere and were monitored by TLC (Merck F254 silica gel). Products were separated by preparative TLC or by liquid chromatography with a Horizon HPFC System (Biotage, Inc.) fitted with Biotage Si 12+M and Si 25+M columns. Melting points were determined with a Kofler hot-stage apparatus. FTIR spectra were recorded with a MIDAC Corporation Spectrafile IR apparatus or with a GENESIS ATI (Unicam) spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^{1}H), 75.47 MHz (^{13}C), and 282.40 MHz (^{19}F) with $CDCl_3$ as solvent. Chemical shifts are reported in ppm, and either tetramethylsilane (δ = 0.00 ppm) or $CHCl_3$ (δ = 7.27 ppm) served as internal standards for ^{1}H NMR analysis, $CDCl_3$ (δ = 77.23 ppm) for ^{13}C NMR analysis, and $CFCl_3$ (δ = 0.00 ppm) for ^{19}F NMR analysis. GC–MS data were obtained with a Trace MS Thermoquest apparatus at 70 eV with electron impact (EI) ionization or with a Shimadzu GC–MS-QP2010 operating in EI mode at 70 eV. MS data were obtained with a Fisons Instruments TRIO 1000 spectrometer at 70 eV in the EI mode and by thermal desorption. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. High-resolution mass spectra (HRMS) were recorded with a Q-TOF Micro micromass instrument in the positive ESI (CV = 30 V) mode. X-ray diffraction data were collected with a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined by full-matrix least-squares methods using the SHELXTL program package.[14,15] Hydrogen atoms were placed in calculated idealized positions.

The preparation of nonsymmetrical allenyl azine **1a** and criss-cross products **2Aa** and **2Da** have been published previously.[2b]

General Procedure for the Synthesis of Criss-Cross Cycloadducts 2 and Unexpected Products 4 and 9: A mixture of allenyl azine **1** (0.25 mmol) and alkyne **A**–**F** (0.5 mmol) in dry xylene (10 mL) was heated under reflux for the time given for each compound. The solvent was then removed under vacuum and the residue was separated either by preparative TLC or by HPFC on silica gel. The solvents used are indicated for each compound. Bicyclic products **4** were formed only in the reactions with alkynes **E** and **F** with pronounced "push–pull" systems, whereas products **9** were obtained only from the reactions of fluorinated allenyl azines **1a** and **1b** with alkyne **F**.

Ethyl 2,5,5-Trimethyl-4-methylene-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]-pyrazole-3-carboxylate (4a): Yield 16 mg, 27% (16.5 h; from fluorinated allenyl azine **1a**) and 20 mg, 34% (24 h; from non-fluorinated allenyl azine **1c**); white solid; m.p. 88.5–90.0 °C. R_f = 0.60 (AcOEt/PE, 1:2). ^{1}H NMR: δ = 6.44 (s, 1 H, =CH_2), 5.31 (s, 1 H, =CH_2), 4.33 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 3.95 (s, 2 H, N-CH_2), 2.50 (s, 3 H, =CCH_3), 1.38 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_2CH_3), 1.36 (s, 6 H, H_3CCCH_3) ppm. ^{13}C NMR: δ = 164.5 (s, C=O), 157.0 (s, N=C), 147.4 (s, *C*=CH_2), 145.9 (s, NC=), 111.0 (s, =CH_2), 105.9 (s, *C*C=O), 61.2 (s, NCH_2), 60.1 (s, *C*H_2CH$_3$), 46.2 (s, H_3C*C*CH$_3$), 28.7 (s, H_3*C*C*C*H$_3$), 15.1 (s, =C*C*H$_3$), 14.7 (s, CH_2*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1107, 1160, 1290, 1391, 1474, 1707 (C=O), 2873, 2931, 2967 cm^{-1}. GC–MS: *m*/*z* (%) = 234 (74) [M$^+$], 189 (100), 175 (38). HRMS: calcd. for $C_{13}H_{19}N_2O_2^+$ 235.1447; found 235.1442. $C_{13}H_{18}N_2O_2$ (234.29): calcd. C 66.64, H 7.74, N 11.96; found C 66.47, H 7.83, N 11.89.

Ethyl 4-Ethylidene-2,5,5-trimethyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]-pyrazole-3-carboxylate (4b): Yield 21 mg, 34% (16.5 h; from the fluorinated allenyl azine **1b**) and 23 mg, 37% (24 h; from non-fluorinated allenyl azine **1d**); colorless oil. R_f = 0.16 (AcOEt/PE, 1:4). Isomer ratio ca. 5:1. ^{1}H NMR (major isomer): δ = 5.62 (q, $^3J_{H,H}$ = 7.3 Hz, 1 H, =C*H*CH$_3$), 4.30 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 3.84 (s, 2 H, NCH_2), 2.45 (s, 3 H, =CCH_3), 1.83 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, =CHCH_3), 1.35 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_2CH_3), 1.29 (s, 6 H, H_3CCCH_3) ppm. ^{13}C NMR: δ = 164.7 (s, C=O), 154.9 (s, N=C), 145.6 (s, NC=), 137.7 (s, *C*=CHCH$_3$), 121.6 (s, =*C*HCH$_3$), 107.5 (s, *C*C=O), 60.9 (s, NCH_2), 60.2 (s, *C*H_2CH$_3$), 47.9 (s, H_3C*C*CH$_3$), 27.3 (s, H_3*C*C*C*H$_3$), 17.0 (s, =C*C*H$_3$), 14.8 (s, =CH*C*H$_3$), 14.6 (s, CH_2*C*H$_3$) ppm. HRMS: calcd. for $C_{14}H_{21}N_2O_2^+$ 249.1603; found 249.1603. ^{1}H NMR (minor isomer): δ = 7.28 (q, $^3J_{H,H}$ = 7.7 Hz, 1 H, =C*H*CH$_3$), 4.29 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 3.92 (s, 2 H, NCH_2), 2.45 (s, 3 H, =CCH_3), 1.96 (d, $^3J_{H,H}$ = 7.7 Hz, 3 H, =CHCH_3), 1.48 (s, 6 H, H_3CCCH_3), 1.36 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 164.8 (s, C=O), 156.7 (s, N=C), 149.9 (s, NC=), 137.3 (s, *C*=CHCH$_3$), 126.1 (s, =*C*HCH$_3$), 105.1 (s, *C*C=O), 63.1 (s, *C*H_2CH$_3$), 60.0 (s, NCH_2), 45.7 (s, H_3C*C*CH$_3$), 27.4 (s, H_3*C*C*C*H$_3$), 17.0 (s, =C*C*H$_3$), 15.4 (s, =CH*C*H$_3$), 14.3 (s, CH_2*C*H$_3$) ppm. IR (film): $\tilde{\nu}_{max}$ = 1107, 1138, 1173, 1277, 1375, 1446, 1466, 1540, 1709 (C=O), 2875, 2933, 2978 cm^{-1}. GC–MS: *m*/*z* (%) = 248 (41) [M]$^+$, 202 (100), 187 (82). HRMS: calcd. for $C_{14}H_{21}N_2O_2^+$ 249.1603; found 249.1594.

Ethyl 5,5-Dimethyl-4-methylene-2-phenyl-5,6-dihydro-4*H*-pyrrolo-[1,2-*b*]pyrazole-3-carboxylate (4c): Yield 13 mg, 17% (16.5 h; from fluorinated allenyl azine **1a**) and 22 mg, 30% (24 h; from non-fluorinated allenyl azine **1c**); white solid; m.p. 81.0–82.0 °C. R_f = 0.11 (AcOEt/PE, 1:9). ^{1}H NMR: δ = 7.50–7.60 (m, 2 H, Ph), 7.28–7.33 (m, 3 H, Ph), 6.42 (s, 1 H, =CH_2), 5.30 (s, 1 H, =CH_2), 4.16 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 3.98 (s, 2 H, NCH_2), 1.34 (s, 6 H, H_3CCCH_3), 1.14 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 164.0 (s, C=O), 158.8 (s, N=C), 147.7 (s, *C*=CH_2), 145.9 (s, NC=), 133.6 (s, C, Ph), 129.6 (s, 2× CH, Ph), 128.4 (s, CH, Ph), 127.8 (s, 2× CH, Ph), 111.4 (s, =CH_2), 105.6 (s, *C*C=O), 61.4 (s, NCH_2), 60.3 (s, *C*H_2CH$_3$), 46.3 (s, H_3C*C*CH$_3$), 28.8 (s, H_3*C*C*C*H$_3$), 14.3 (s, CH_2*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1049, 1168, 1305, 1449, 1528, 1691 (C=O), 2866, 2928, 2960 cm^{-1}. GC–MS: *m*/*z* (%) = 296 (100) [M]$^+$, 251 (93), 224 (35), 77 (23). HRMS: calcd. for $C_{18}H_{21}N_2O_2^+$ 297.1603; found 297.1607.

Ethyl 4-Ethylidene-5,5-dimethyl-2-phenyl-5,6-dihydro-4*H*-pyrrolo-[1,2-*b*]pyrazole-3-carboxylate (4d): Yield 26 mg, 34% (16.5 h; from fluorinated allenyl azine **1b**) and 30 mg, 39% (24 h; from non-fluorinated allenyl azine **1d**); white solid; m.p. 98.5–100.5 °C. R_f = 0.06 (AcOEt/PE, 5:95). Isomer ratio ca. 3:1. ^{1}H NMR (major isomer): δ = 7.58–7.65 (m, 2 H, Ph), 7.30–7.37 (m, 3 H, Ph), 5.65 (q, $^3J_{H,H}$ = 7.1 Hz, 1 H, =C*H*CH$_3$), 4.22 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.97 (s, 2 H, NCH$_2$), 1.82 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, =CHC*H*$_3$), 1.35 (s, 6 H, H$_3$CCCH$_3$), 1.18 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR: δ = 165.5 (s, C=O), 155.9 (s, N=C), 145.0 (s, NC=), 137.9 (s, *C*=CHCH$_3$), 133.5 (s, C, Ph), 128.8 (s, 2× CH, Ph), 128.3 (s, CH, Ph), 128.1 (s, 2× CH, Ph), 120.9 (s, =*C*HCH$_3$), 107.4 (s, *C*C=O), 61.1 (s, NCH$_2$), 60.9 (s, *C*H$_2$CH$_3$), 47.5 (s, H$_3$C*C*CH$_3$), 27.8 (s, H$_3$*C*C*C*H$_3$), 16.5 (s, =CH*C*H$_3$), 14.2 (s, CH$_2$*C*H$_3$) ppm. ^{1}H NMR (minor isomer): δ = 7.58–7.65 (m, 2 H, Ph), 7.30–7.37 (m, 3 H, Ph), 7.28 (q, $^3J_{H,H}$ = 7.7 Hz, 1 H, =C*H*CH$_3$), 4.16 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 4.03 (s, 2 H, NCH$_2$), 2.00 (d, $^3J_{H,H}$ = 7.7 Hz, 3 H, =CHC*H*$_3$), 1.53 (s, 6 H, H$_3$C-C-CH$_3$), 1.12 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR δ = 164.5 (s, C=O), 158.6 (s, N=C), 149.5 (s, NC=), 137.1 (s, *C*=CHCH$_3$), 134.1 (s, C, Ph), 129.6 (s, 2× CH, Ph), 128.2 (s, CH, Ph), 127.7 (s, 2× CH, Ph), 126.2 (s, =*C*HCH$_3$), 104.7 (s, *C*C=O), 63.2 (s, *C*H$_2$CH$_3$), 60.2 (s, NCH$_2$), 45.9 (s, H$_3$C*C*CH$_3$), 27.5 (s, H$_3$*C*C*C*H$_3$), 14.4 (s, =CH*C*H$_3$), 14.1 (s, CH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1053, 1161, 1283, 1371, 1443, 1541, 1707 (C=O), 2868, 2930, 2962, 2978 cm^{-1}. GC–MS: *m*/*z* (%) = 310 (60) [M]$^+$, 264 (82), 249 (100), 77 (23). HRMS: calcd. for $C_{19}H_{23}N_2O_2^+$ 311.1760; found 311.1760.

(3*S,4*R**)-Ethyl 4,4,5-Trimethyl-2-phenyl-6-(3,3,3-trifluoro-2-methylpropenyl)-3a,4-dihydro-3*H*-pyrrolo[1,2-*b*]pyrazole-3-carboxylate (9a):** Yield 56 mg, 55% (16.5 h); white solid; m.p. 112.5–116.0 °C. R_f = 0.20 (AcOEt/PE, 1:9). ^{19}F NMR: δ = –69.5 (s) ppm. ^{1}H NMR: δ = 7.55–7.65 (m, 2 H, Ph), 7.20–7.35 (m, 3 H, Ph), 6.55 (br. s, 1 H, CH=CCF$_3$), 4.32 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H, CHC=O), 4.25 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H, NCH), 4.07 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 2.09 (s, 3 H, H$_3$CCCF$_3$), 1.59 (s, 3 H, =CCH$_3$), 1.11 (s, 3 H, H$_3$CCC*H*$_3$), 1.08 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 0.91 (s, 3 H, *H*$_3$CCCH$_3$) ppm. ^{13}C NMR: δ = 171.0 (s, C=O), 150.9 (s, N=C), 136.1 (s, NC=), 134.7 (s, =*C*CH$_3$), 131.6 (s, C, Ph), 129.4 (s, CH, Ph), 128.6 (s, 2× CH, Ph), 127.4 (q, $^2J_{C,F}$ = 28.5 Hz, *C*CF$_3$), 126.8 (s, 2× CH, Ph), 125.0 (q, $^1J_{C,F}$ = 273.0 Hz, CF$_3$), 120.6 (q, $^3J_{C,F}$ = 6.6 Hz, *C*H=CCF$_3$), 77.4 (s, NCH), 61.8 (s, *C*H$_2$CH$_3$), 52.7 (s, *C*HC=O), 47.1 (s, H$_3$C*C*CH$_3$), 26.8 (s, H$_3$CC*C*H$_3$), 23.6 (s, H$_3$*C*CCH$_3$), 14.1 (s, CH$_2$*C*H$_3$), 12.9 (q, $^3J_{C,F}$ = 1.1 Hz, H$_3$*C*CCF$_3$), 9.5 (s, =C*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1097, 1160, 1297, 1729 (C=O), 2870, 2932, 2966 cm^{-1}. GC–MS: *m*/*z* (%) = 406 (100) [M]$^+$, 391 (32), 333 (71), 230 (51), 103 (41). $C_{22}H_{25}F_3N_2O_2$ (406.44): calcd. C 65.01, H 6.20, N 6.89; found C 64.94, H 6.31, N 6.78.

(3*S,4*R**)-Ethyl 5-Ethyl-4,4-dimethyl-2-phenyl-6-(3,3,3-trifluoro-2-methylpropenyl)-3a,4-dihydro-3*H*-pyrrolo[1,2-*b*]pyrazole-3-carboxylate (9b):** Yield 18 mg, 17% (16.5 h); white solid; m.p. 97.5–101.0 °C. R_f = 0.11 (AcOEt/PE, 5:95). ^{19}F NMR: δ = –65.5 (s) ppm. ^{1}H NMR: δ = 7.69–7.73 (m, 2 H, Ph), 7.30–7.38 (m, 3 H, Ph), 6.32–6.35 (m, 1 H, CH=CCF$_3$), 4.37 (d, $^3J_{H,H}$ = 3.9 Hz, 1 H, CHC=O), 4.32 (d, $^3J_{H,H}$ = 3.9 Hz, 1 H, NCH), 4.17 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 2.08–2.18 (m, 1 H, =CC*H*$_2$CH$_3$), 2.04 (d, $^4J_{H,H}$ = 1.5 Hz, 3 H, H$_3$CCCF$_3$), 1.90–2.00 (m, 1 H, =CC*H*$_2$CH$_3$), 1.22 (s, 3 H, H$_3$CCC*H*$_3$), 1.17 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.01 (t, $^3J_{H,H}$ = 7.6 Hz, 3 H, =CCH$_2$C*H*$_3$), 1.00 (s, 3 H, *H*$_3$CCCH$_3$) ppm. ^{13}C NMR: δ = 171.5 (s, C=O), 150.9 (s, N=C), 134.7 (s, NC=), 133.5 (s, =*C*CH$_2$CH$_3$), 132.0 (s, C, Ph), 130.6 (q, $^2J_{C,F}$ = 29.6 Hz, *C*CF$_3$), 129.3 (s, CH, Ph), 128.6 (s, 2× CH, Ph), 126.8 (s, 2× CH, Ph), 126.2 (q, $^3J_{C,F}$ = 3.3 Hz, *C*H=CCF$_3$), 123.7 (q, $^1J_{C,F}$ = 275.0 Hz, CF$_3$), 78.1 (s, NCH), 61.8 (s, OC*H*$_2$CH$_3$), 53.1 (s, *C*HC=O), 48.0 (s, H$_3$C*C*CH$_3$), 27.1 (s, H$_3$*C*CCH$_3$), 24.4 (s, H$_3$CC*C*H$_3$), 18.8 (q, $^3J_{C,F}$ = 1.3 Hz, F$_3$CC*C*H$_3$), 17.8 (s, =C*C*H$_2$CH$_3$), 14.4 (s, =CCH$_2$*C*H$_3$), 14.2 (s, OCH$_2$*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1114, 1167, 1273, 1293, 1386, 1736 (C=O), 2873, 2933, 2967 cm^{-1}. GC–MS: *m*/*z* (%) = 420 (100) [M]$^+$, 405 (82), 347 (92), 333 (24), 244 (52), 174 (27), 145 (40), 103 (76), 91 (28), 77 (37). HRMS: calcd. for $C_{23}H_{28}F_3N_2O_2^+$ 421.2103; found 421.2090.

Supporting Information (see also the footnote on the first page of this article): Isolated heterocyclic products, experimental details and spectroscopic data for allenyl azines **1** and criss-cross products **2** with some ^{1}H NMR spectra and crystal structures.

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[1] a) N. Krause, A. S. K. Hashmi, in: *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**, vol. 1 and 2; b) R. Zimmer, *Synthesis* **1993**, 165–168; c) B. A. Trofimov, *J. Heterocycl. Chem.* **1999**, *36*, 1469–1490; d) L. Brandsma, *Eur. J. Org. Chem.* **2001**, 4569–4581; e) L. Brandsma, N. A. Nedolya, *Synthesis* **2004**, 735–745; f) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45–56.

[2] a) S. Man, P. Kulhánek, M. Potáček, M. Nečas, *Tetrahedron Lett.* **2002**, *43*, 6431–6433; b) S. Man, J.-P. Bouillon, M. Nečas, M. Potáček, *Tetrahedron Lett.* **2004**, *45*, 9419–9421; c) S. Man, M. Nečas, J.-P. Bouillon, H. Baillia, D. Harakat, M. Potáček, *Tetrahedron* **2005**, *61*, 2387–2393; d) S. Man, M. Nečas, J.-P. Bouillon, C. Portella, M. Potáček, *Eur. J. Org. Chem.* **2006**, 3473–3478; e) J. Galeta, S. Man, M. Potáček, *Arkivoc* **2009**, *6*, 245–259.

[3] R. Marek, I. Šťastná-Sedláčková, J. Toušek, J. Marek, M. Potáček, *Bull. Soc. Chim. Belg.* **1997**, *106*, 645.

[4] A. Koziara, K. Turski, A. Zwierzak, *Synthesis* **1986**, 298–301.

[5] a) J. R. Bailey, N. H. Moore, *J. Am. Chem. Soc.* **1917**, *39*, 279–291; b) J. R. Bailey, A. T. McPherson, *J. Am. Chem. Soc.* **1917**, *39*, 1322–1338.

[6] R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598.

[7] A. Padwa, in: *1,3-Dipolar Cycloaddition Chemistry*, John Wiley & Sons, New York, **1984**.

[8] A. Gieren, P. Narayanan, K. Burger, W. Thenn, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 475–476.

[9] P. Kulhánek, M. Potáček, J. Koča, *Collect. Czech. Chem. Commun.* **2004**, *69*, 231–241.

[10] L. Davis, G. Kuttan, *Immunopharmacol. Immunotoxicol.* **1999**, *21*, 695–703.

[11] B. Singh, A. K. Saxena, B. K. Chandan, D. K. Gupta, K. K. Bhutani, K. K. Anand, *Phytother. Res.* **2001**, *15*, 311–318.

[12] L. Davis, G. Kuttan, *J. Exp. Clin. Cancer Res.* **2002**, *21*, 115–118.

[13] B. C. Hamper, *Org. Synth.* **1992**, *70*, 246–255.

[14] *SHELXTL*, version 5.10, Bruker AXS Inc., Madison, WI, USA, **1997**.

[15] CCDC-773515 (for **2Dc**), -773516 (for **2Ea$_2$**), -773517 (for **4c**), -773518 (for **4d**), -773519 (for **9a**), and -773520 (for **9b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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