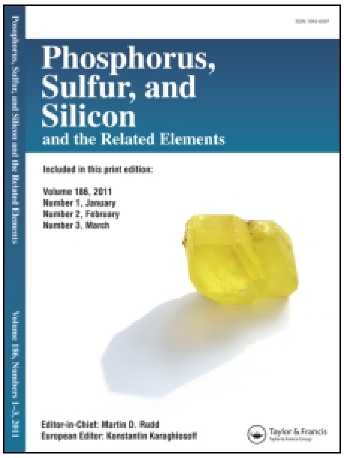

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Synthesis, Structure, and *In Vitro* Anti-HIV Activity of New Pyrazole, 1,2,4-Thiadiazole, and 1,2,4-Triazole Derivatives

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Synthesis, Structure, and *In Vitro* Anti-HIV Activity of New Pyrazole, 1,2,4-Thiadiazole, and 1,2,4-Triazole Derivatives

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*α,α′-Dichloroazo compounds **6** react with Lewis acid to furnish 1-(chloroalkyl)-1-aza-2-azoniaallene salts **4**. The cations **4** react with acetylenes, isothiocyanates, isocyanates, and carbodiimides under [3+2]-cycloaddition. The cycloadducts undergo consecutive reactions, e.g., [1,2]-shifts of alkyl groups. The newly synthesized products were evaluated for their anti-HIV-1 and anti-HIV-2 activity in MT-4 cells.*

Keywords 1,2,4-Thiadiazolse; 1,2,4-Triazole; NNRTIs; pyrazoles; synthesis

INTRODUCTION

HIV-1 reverse transcriptase (RT) is a key enzyme in HIV replication as well as a key target for developing anti-HIV drugs. Two types of reverse transcriptase inhibitor have been developed;[1–3] nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Three NNRTIs, nevirapine,[4] delaviridine,[5,6] and efavirenz[7] have been approved by the Food and Drug Administration (FDA) for the treatment of HIV infection; however, significant resistance has developed against the current NNRTIs and there is an urgent need to develop new anti-HIV agents that are effective against resistant mutants.[8,9] Several potent heterocyclic NNRTIs have been synthesized with high anti-HIV inhibitory activity, some of which have an pyrazole scaffold.[10] Moreover, numerous examples of pyrazoles have been reported with a range of biological activities

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including antipyretic[11] and antidepressant[12] activities. Important application of pyrazoles derivatives as antibiotics has also been reported.[13,14] In addition, several 1,3,4-thiadiazole nucleus constitutes the active part of several biologically active compounds, including antimycotic[15,16] and anti-inflammatory agents.[17–19] Moreover, 1,2,4-triazole moiety is present, for example, in certain antiasthmatic,[20] antiviral (ribavirin),[21] antifungal (fluconazole),[22] antibacterial,[23] and hypnotic (triazolam)[24] drugs. Based on the above reports, and in continuation of our research on the synthesis of biologically active heterocyclic molecules, the synthesis and anti-HIV evaluation of the title compounds are reported.

RESULTS AND DISCUSSION

Chemistry

Jochims et al.[25–29] described synthesis of 1-aza-2-azoniaallene salts **1**. These salts undergo cycloaddition to many types of multiple bonds (alkenes, nitriles, alkynes, isothiocyanates, isocyanates, and carbodiimides) to afford heterocyclic salts. Cycloaddition of **1** suffers from the disadvantage that one ends up with salts. For applications, electrically neutral to circumvent this problem, we tried to prepare heterocumulenes **1** substituted with a leaving group R^3 (e.g., $CClR^1R^2$) which can finally be removed from the cycloadduct **2** and **3** (Figure 1).

Recently, we reported polar [3+2]-cycloadditons of 1-aza-2-azoniaallene cations, **4** to nitriles, we synthesized a variety of

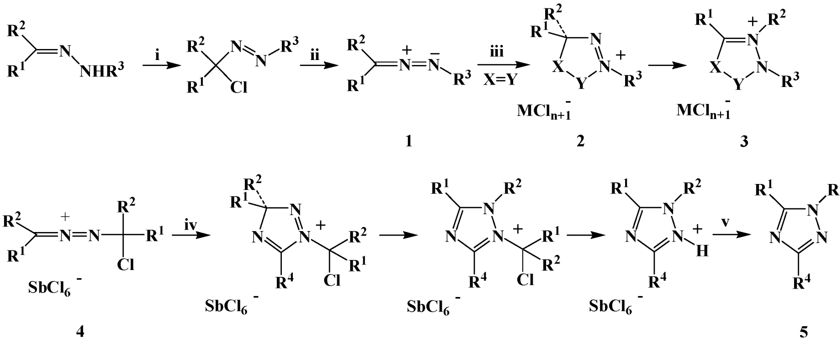
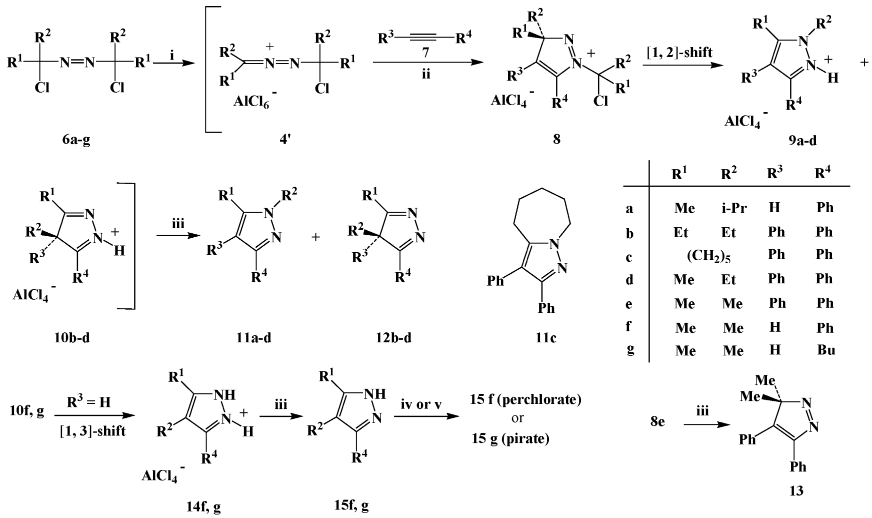


FIGURE 1 Reagents and conditions: i. t-BuOCl, $CHCl_3$; ii. MCl_n ($SbCl_5$, $TiCl_4$, $SnCl_4$), CH_2Cl_2, −60°C; iii. X = Y (alkenes, alkynes, nitriles, isocyanates, carbodiimides); R^1, R^2 = alkyl, aryl, CO_2R, *tert*-butyl), −60°C to 23°C; iv. R^4CN, −60°C to 23°C; and v. $NaHCO_3$, NH_3, MeCN, H_2O, 0°C, 2 h.



	R^1	R^2	R^3	R^4
a	Me	i-Pr	H	Ph
b	Et	Et	Ph	Ph
c	$(CH_2)_5$		Ph	Ph
d	Me	Et	Ph	Ph
e	Me	Me	Ph	Ph
f	Me	Me	H	Ph
g	Me	Me	H	Bu

FIGURE 2 Reagents and conditions: i. $AlCl_3$, CH_2Cl_2, −60°C; ii. −60°C to 23°C; iii. $NaHCO_3$, NH_3, MeCN, H_2O, 0°C, 2 h; iv. picric acid in EtOH; and v. $NaClO_4$ in MeCN.

1,5-dialkyl-1H-1,2,4-triazoles **5** (Figure 1) bearing different precursors such as C-nucleosides,[30] acyclic C-nucleosides,[31] pyrimidines,[32] N-alkylphthalimides,[33] D-mannopentitol-1-yl-1,2,4-triazoles,[34] 1H-indoles,[35] quinolones,[35] benzotriazoles,[36] 3′-triazolo-thymidines,[37] acetic acid alkylidene hydrazides,[38] 1,4-disubstituted piperazines,[39,40] and thiophenes.[41]

Here, we report that [3+2]-cycloadditons of cations **4** are not limited to nitriles but can be carried out with many types of multiple bonds.

The reactive intermediates **4′** (Figure 2) were obtained from the α,α'-di-chloroazo compounds **6a–g**[42,43] by the treatment with $AlCl_3$ at −60°C. At approximately −30°C, the color changed from orange to brown, indicating that cumulenes **4′a–g** underwent cycloaddition reactions with acetylenes **7a–g** to give the pyrazolium salts **9** or **10** via 3*H*-pyrazolium salts **8**. With asymmetric acetylenes, the cycloadditions occurred with complete regioselectivity.

Alkyl and aryl mono- and disubstituted acetylens can be used. However, electron-deficient acetylenes—e.g., acetylenedicarboxlic acid dimethylester—did not react with **4′**. The use of antimony pentachloride as Lewis acid often led to tarry products. Apparently, the acetylenes were oxidatively destroyed by $SbCl_5$. No such decomposition was encountered with $AlCl_3$ as the Lewis acid.

The scope of the reaction is limited by the fact that the primarily formed 3*H*-pyrazolium salts **8** rearrange to mixtures of 1*H*- and 4*H*-pyrazolium salts **9** and **10**. In situ hydrolysis of **9** and **10** with aqueous $NaHCO_3$ and aqueous NH_3, afforded the pyrazoles **11** and **12** respectively. Thus, from the cumulene **4′a** and phenylacetylene (**7a**), only the 1*H*-pyrazoles **11a** was obtained in 48% yield. However, the cumulenes **4′b–d** and diphenylacetylene give a mixture of **11b–d** and **12b–d** in 84–91% yield, which separated by column chromatography. Finally, from the cation **4′e** and diphenylacetylene the 3*H*-pyrazolium salt **8e** was formed exclusively, which hydrolyzed to 3*H*-pyrazole **13** in 72% yield. Interestingly, for cation **8e**, the [1, 2]-shift of R^2 (R^2 = methyl) not observed.

With monosubstituted acetylenes (R^3 = H) the intermediate 4*H*-pyrazolium salts **10** could not be obtained. Instead, 1*H*-pyrazolium salts **14** resulting from a [1, 3]-prototropic rearrangement of **10** were isolated and characterized as their perchlorates or picrates. Again, from the intermediates **4′f** and **4′g** only the salts **14f** and **14g** were isolated, which hydrolyzed to 1*H*-pyrazoles **15f** and **15g** and characterized as perchlorate and picrate in 85 and 76% yield, respectively.

The constitutions of compounds **11–13** were easily derived from the NMR spectra. For instance, the ^{1}H NMR spectrum (recorded in $CDCl_3$) of the pyrazole **11c** showed multiplet for NCH_2 at $\delta = 4.36$ together with five multiplets for C-CH_2 groups ($\delta = 1.69$–2.71) bound directly to the heterocyclic ring. The ^{13}C-NMR resonances for C(4) and C = N of compounds **12a–d** appear at $\delta = 72.3$–72.6 and $\delta = 176.7$–184.4, respectively.

Addition of isothiocyanates **16a**,**b** to the reactive intermediate **4″**, which prepared from α,α'-di-chloroazo compound **6** ($R^1 = R^2 =$ Me)[42,43] by the treatment with $SbCl_5$ at −60°C. By employing the methods of Jochims et al.,[44] lead to a color change of the orange suspension of **4″** between −60°C and +23°C indicating a cycloaddition reaction. The resulting 1,3,4-thiadiazole **17a**,**b** lost its CMe_2Cl group and furnished the moderately stable iminium salts **18a**,**b** (Figure 3), the presence of traces of moisture in the reaction mixtures is likely to be responsible for these results. Imine**19a**,**b** was obtained by hydrolysis of the salts **18a**,**b** in 85 and 76% yield, respectively. Correspondingly, from allene **4″** the heterocycle **19c** were prepared in 77% yield.

The concerted cycloadditions to isothiocyanates are known to occur both on the C=S and the C=N bond in a competitive manner.[44] The isothiocyanate group of compound **16** reacts as *S*-nucleophile resulting in 2,5-dihydro-1,3,4-thiadiazole **19** and not as *N*-nucleophile, which would have resulted in an isomeric 4,5-dihydro-1*H*-1,3,4-triazole-5-thione.

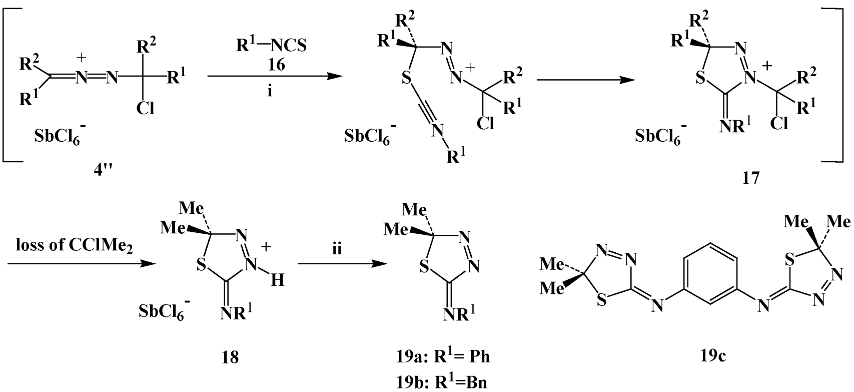


FIGURE 3 Reagents and conditions: i. CH_2Cl_2, −60°C to 23°C; and ii. $NaHCO_3$, NH_3, MeCN, H_2O, 0°C, 2 h.

Compounds **19a–c** were identified from the ^{1}H-NMR and ^{13}C-NMR spectra, which are in agreement with those of thiadiazole analogous obtained by Jochims et al.[44] The ^{1}H NMR spectrum of **19c** (recorded in $CDCl_3$) is characterized by the presence of singlet at $\delta = 1.88$, which were attributed to the four methyl groups. The ^{13}C NMR shifts at $\delta = 107.3$ and 175.1 observed for **19c** are assigned to the sp^3 hybridized ring carbon atom C(5) and C(2) of the thiadiazole ring, and at $\delta = 28.3$ attributed to the methyl on C(5).

From the hexachloroantimonate **4**″ and isocyanate **20** (Figure 4), the triazolium salts **21** was formed exclusively. It is noteworthy that the isocyanate acted as a nucleophilic in this reaction,[28] the [1, 2]-shift of R^2 (R^2 = methyl) not observed. The resulting 1,2,4-triazolium salts **21** lost its CMe_2Cl group and afforded salts **22**, which hydrolyzed to furnished the neutral 5-oxo-4,5-dihydro-3*H*-1,2,4-triazole derivatives **23**. The structures of the compounds **23a–c** were confirmed by the ^{1}H-, ^{13}C-NMR, and mass spectra. The ^{1}H NMR spectrum of **23c** (recorded in $CDCl_3$) is characterized by the presence of singlet at $\delta = 1.59$, which were attributed to the two methyl groups. The ^{13}C-NMR shifts at $\delta = 161.5$ observed for **23c** is assigned to C = O.

Finally, cycloaddition of carbodiimides **24** to heteroallen **4**″ provided the triazolium salts **25**, which lost its CMe_2Cl group to furnish the iminium salts**26**. Neutralization of salts **26** with aqueous $NaHCO_3$ and aqueous NH_3, afforded the 3*H*-1,2,4-triazoles **27** (Figure 5). The structure of **27a–c** was determined from the ^{1}H, ^{13}C NMR and mass spectrum.

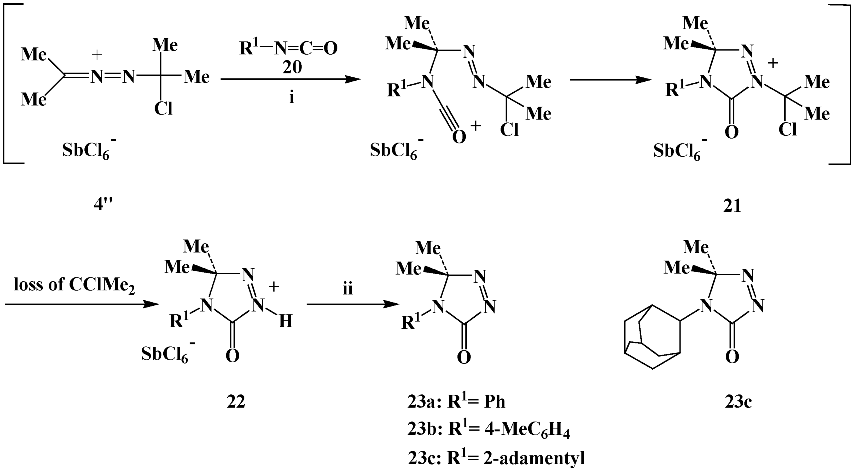
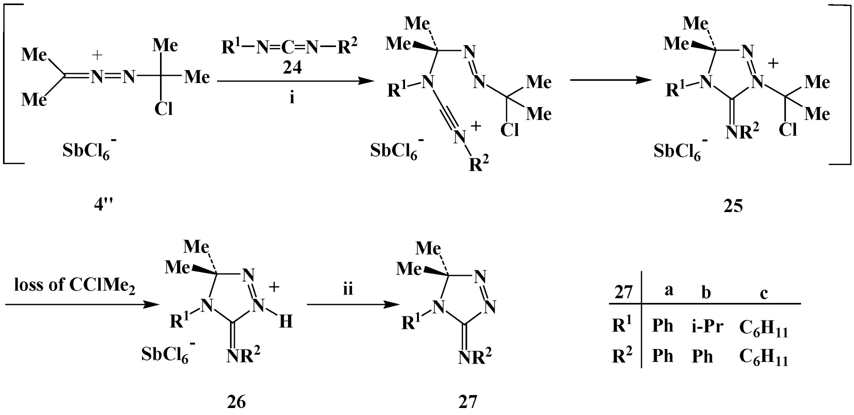


FIGURE 4 Reagents and conditions: i. CH_2C1_2, −60°C to 23°C; ii. $NaHCO_3$, NH_3, MeCN, H_2O, 0°C, 2 h.

In-Vitro Anti-HIV Assay

Compounds **11b,c**, **13**, **15g**, **19a**, **19c**, **23a**, and **27a,b** were tested for their in vitro anti-HIV-1 (strain IIIB) and anti-HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay.[45] The antiviral activity was compared with that of the known and approved antiviral drugs efavirenz[7] and capravirine.[46] The results



27	a	b	c
R^1	Ph	i-Pr	C_6H_{11}
R^2	Ph	Ph	C_6H_{11}

FIGURE 5 Reagents and conditions: i. CH_2C1_2, −60°C to 23°C; ii. $NaHCO_3$, NH_3, MeCN, H_2O, 0°C, 2 h.

TABLE I *In vitro* Anti-HIV-1[a] and HIV-2[b] of Some New Heterocycles

Compound	Virus strain	EC_{50} (μg/mL)[c]	CC_{50} (μg/mL)[d]	SI[e]
11b	III_B	>3.4	3.88 ± 0.39	<1
	ROD	>3.7	3.88 ± 0.39	<1
11c	III_B	>2.1	2.27 ± 0.11	<1
	ROD	>2.3	2.27 ± 0.11	<1
13	III_B	>11.7	12.40 ± 1.72	<1
	ROD	>11.0	2.27 ± 1.72	<1
15f	III_B	>63.1	62.60 ± 1.69	<1
	III_B	>59.8	62.60 ± 1.69	<1
19a	III_B	>10.1	9.66 ± 0.96	<1
	ROD	>8.3	9.66 ± 1.69	<1
19c	III_B	>47.0	57.53 ± 11.10	<1
	ROD	>56.0	57.53 ± 11.10	<1
23a	III_B	>57.1	55.80 ± 3.36	<1
	ROD	>50.8	55.80 ± 3.36	<1
27a	III_B	>65.0	65.95 ± 4.74	<1
	ROD	>60.6	65.95 ± 4.74	<1
27b	III_B	>65.2	68.85 ± 3.64	<1
	III_B	>65.2	68.85 ± 3.64	<1
Efavirenz[7]	III_B	0.003	40	13,333
Capravirine[46]	III_B	0.0014	11	7,857

[a] Anti-HIV-1 activity measured with strain III_B. [b] Anti-HIV-2 activity measured with strain ROD. [c] Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect. [d] Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%. [e] SI: Selectivity index (CC_{50}/EC_{50}).

are summarized in Table I. All tested compounds proved to be less active than efavirenz and capravirine. None of the tested compounds was found to inhibit HIV-1 or HIV-2 replication in vitro at EC_{50} lower than the cytotoxic concentration (CC_{50}), resulting in a selectivity index <1. The structure-activity relationship suggested that pyrazoles manifested a higher HIV inhibitory activity than that of the 1,3,4-thiadiazol or 1,2,4-triazoles. Thus, pyrazole **11c** showed the highest activity (EC_{50} = 2.12 μg/mL), but did not demonstrate selectivity. Such a result would lead us to modify the structures of the pyrazole residue with more potential groups.

EXPERIMENTAL

Materials and Methods

Chemistry melting points were measured on a Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland) and are uncorrected. Microanalytical data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (1H) and on 150.91 MHz (13C) spectrometers (Bruker, Germany) with tetramethylsilane (TMS) as internal standard and on d scale in ppm. Mass spectra were measured on a MAT8200 spectrometer on 70 eV EI.

Cycloaddition of the 1-(1-Chloroalkyl)-1-aza-2-azoniaallene Salts—General Procedures

Method A. solution of $SbCl_5$ (2.99 g, 10 mmol) in CH_2Cl_2 (15 ml) is added dropwise to a cold (−70°C) stirred solution of the azo(1-chloroalkane) **6** (10 mmol) and the unsaturated compounds (isothiocyanates, isocyanates or carbodiimides) in CH_2Cl_2 (50 ml). After stirring between −60°C and −10°C for 2 h and then at 0°C for 10 min the solvent is evaporated. Alternatively, the product is precipitated at 0°C by addition of pentane. The resulting salt is hydrolyzed to furnish the neutral heterocycle.

Method B. A solution of **6** (10 mmol) in CH_2Cl_2 (60 ml) is added dropwise to a cold (−60°C) suspension of $AlCl_3$ (1.34 g, 10 mmol) in CH_2Cl_2 (20 ml). After 5 min, a solution of the alkyne (10 to 12 mmol) in CH_2Cl_2 (20 ml) is added dropwise. The mixture is stirred at −60°C for 1 h and finally at 23°C for 10 min. Evaporation of the solvent affords the very moisture sensitive dark brown oily tetrachloroaluminate, which is hydrolyzed to the neutral heterocycle, or it is transformed into the crystalline perchlorate or picrate.

Hydrolysis

At 0°C a solution of $NaHCO_3$ (8.40 g, 100 mmol) in H_2O (100 ml) containing NH_3 (1.70 g, 100 mmol) is added dropwise to the solution of the crude salts **8e**, **9a–d**, **10b–d**, **14f**,**g**, **18a**,**b**, **18c**, **22a–c**, **26a–c**, in MeCN (100 ml). After stirring at 0°C for 2 h, the organic layer is separated and the aqueous layer is extracted with MeCN (3 × 50 ml). The combined MeCN extracts are concerted under reduced pressure to a volume of ca 30 ml. After the addition of CH_2Cl_2 (100 ml), the water phase is separated, and the organic phase is dried with Na_2SO_4. Filtration after addition of decolorizing carbon and evaporation of the solvent affords the products **13**, **11a–d**, **12b–d**, **15f**,**g**, **19a**,**b**, **19c**, **23a–c**, **27a–c**, respectively, which are purified either by crystallization or by column chromatography.

Formation of the Perchlorate from the Tetrachloroaluminate

The crude tetrachloroaluminate **15f** is dissolved in MeCN (60 ml). After addition of $NaClO_4{\cdot}H_2O$ (1.41 g, 10 mmol) in MeCN (20 ml) the mixture is stirred for 3 h. Filtration and concentration of the filtrate under reduced pressure affords the **15f** (perchlorate), which is purified by recrystallization.

1-Isopropyl-5-methyl-3-phenyl-1H-Pyrazole (11a)

From azo(1-chloro-1,2-dimethylpropane) **6a**[47,48] (2.39 g, 10 mmol) and phenylacetylene (1.23 g, 12 mmol) (method B). However, the oily tetrachloroaluminate **9a** was precipitated from the reaction mixture by addition of pentane (200 ml). Hydrolysis afforded a yellow foam, which was crystallized at – 15°C from pentane to furnish yellow prisms (0.96 g, 48%); m.p. 97–99°C (dec). ^{1}H NMR ($CDCl_3$): δ 1.51 (d, J = 6.6, 6H), 2.30 (CH_3), 4.42 (sept, J = 6.6, CH), 6.28 (H4), 7.21–7.80 (m·s, phenyl). ^{13}C-NMR ($CDCl_3$): δ 11.1, 22.5 (2C) (CH_3), 49.9 (CH), 102.3 (C4), 125.5, 127.1, 128.5, 134.2, 138.1, 149.6 (phenyl, C=). Anal. calcd. for $C_{13}H_{16}N_2$ (200.3): C, 77.96; H, 4.81; N, 8.05. Found: C, 77.66; H, 8.18; N, 13.63; MS: m/z (EI) 200.

1,5-Diethyl-3,4-diphenyl-1H-Pyrazole (11b) and 4,5-Diethyl-3,4-diphenyl-3H-Pyrazole (12b)

From azo(1-chloro-1-ethylpropane) **6b**[42] (2.39 g, 10 mmol) and diphenylacetylene (1.78 g, 10 mmol) (Method B). According to the ^{1}H NMR spectrum, the orange oil obtained (2.38, 86%) after hydrolysis consisted of an 1:1 mixture of **11b** and **12b**. The two products were separated by column chromatography (120 g $SiO_2$for flash chromatography; pentane/Et_2O (7:3) as eluent). Evaporation of the solvent of the faster running product afforded an oil, which crystallized at – 15°C from pentane to furnish **11b** as colorless prisms (1.10 g, 40%); m.p. 79–81°C (dec). ^{1}H NMR ($CDCl_3$): δ 1.11 (t, J = 7.5), 1.51 (t, J = 7.2), (CH_3), 2.58 (q, J = 7.5), 4.14 (q, J = 7.2) (CH_2), 7.14–7.45 (m's, phenyl). ^{13}C-NMR ($CDCl_3$): δ 14.4, 16.0, 17.4, 44.0 (CH_3, CH_2), 117.9, 126.5, 127.0, 127.8, 128.0, 128.4, 130.3, 133.8, 134.5, 142.2, 148.0 (phenyl, C=). Anal. calcd. for $C_{19}H_{20}N_2$ (276.4): C, 82.57; H, 7.29; N, 10.14. Found: C, 82.25; H, 7.11; N, 10.03; MS: m/z (EI) 276.

Concentration of the second fraction of the column chromatography afforded **12b** as orange oil (0.45 g, 16%). ^{1}H NMR ($CDCl_3$): δ 0.54 (t, J = 7.4), 1.18 (t, J = 7.2), (CH_3), 2.04–2.44 (m's, 2 CH_2), 7.09–7.65 (m's, 10 H, phenyl). ^{13}C-NMR ($CDCl_3$): δ 7.7, 10.4, 20.1, 24.7 (CH_3, CH_2), 72.9 (C4), 125.9, 127.8, 128.1, 128.6, 129.5, 130.7, 135.3, 176.7, 183.7 (phenyl, C=). Anal. calcd. for $C_{19}H_{20}N_2$ (276.4): C, 82.57; H, 7.29; N, 10.14. Found: C, 82.32; H, 7.12; N, 9.88; MS: m/z (EI) 276.

5,6,7,8-Tetrahydro-2,3-diphenyl-4H-Pyrazolo[1,5-a]azepine (11c) and 3a,4,5,6,7,8-Hexahydro-3,3a-diphenylcycloheptapyrazole (12c)

From azo(1-chlorocyclohexane) **6c**[42,43] (2.63 g, 10 mmol) and diphenylacetylene (1.78 g, 10 mmol) (Method B). For complete hydrolysis of the brown tetrachloroaluminates **9c**, **10c** the mixture in $MeCN/NaHCO_3/NH_3/H_2O$ had to be stirred at 0°C for 4 h and at 23°C for another 24 h. Workup afforded a mixture of **11c** and **12c** (ca 2:1 according to the ^1H NMR spectrum) as orange oil (2.63, 91%). The products were separated by column chromatography (150 g SiO_2 for flash chromatography, Et_2O as eluent). Evaporation of the solvent of the faster running product afforded **11c** as colorless needles (1.66 g, 58%); m.p. 101–103°C (dec). ^1H NMR ($CDCl_3$): δ 1.69 (m, 2H), 1.87 (m, 4H), 2.71 (m, 2H), 4.36 (m, 2H) (CH_2), 7.15–7.43 (m's, 10H, phenyl). ^{13}C NMR ($CDCl_3$): δ 24.6, 27.0, 28.1, 31.0, 53.4 (CH_2), 118.6, 126.5, 127.0, 127.9, 128.1, 128.4, 130.5, 133.7, 134.3, 143.0, 146.9 (phenyl, C=). Anal. calcd. for $C_{20}H_{20}N_2$ (288.4): C, 83.30; H, 6.99; N, 9.71. Found: C, 83.18; H, 6.96; N, 9.61; MS: m/z (EI) 288.

Concentration of the second fraction of the column chromatography afforded **12c** as orange powder (0.39 g, 14%), which was crystallized at −15°C from pentane to furnish a pale yellow crystalline powder; m.p. 113–114°C (dec). ^1H-NMR ($CDCl_3$): δ 1.03–1.16 (m, 1H), 1.50–1.89 (m, 5H), 2.10 (m, 1H), 2.30 (m, 1H), 2.57 (m, 1H), 2.92 (m, 1H) (CH_2), 7.15–7.63 (m's, 10H, phenyl). ^{13}C NMR ($CDCl_3$): δ 24.4, 27.4, 27.5, 29.4, 30.4 (CH_2), 72.3, C3a), 126.5, 128.1, 128.2, 128.5, 129.5, 129.8, 130.5, 134.0 (phenyl), 178.3, 184.4 (C=N). Anal. calcd. for $C_{20}H_{20}N_2$ (288.4): C, 83.30; H, 6.99; N, 9.71. Found: C, 83.28; H, 6.96; N, 9.76; MS: m/z (EI) 288.

1-Ethyl-5-methyl-3,4-diphenyl-1H-Pyrazole (11d) and 4-Ethyl-5-methyl-3,4-diphenyl-4H-Pyrazole (12d)

From azo(1-chloro-1-metylpropane) **6d**[42] (2.11 g, 10 mmol) and diphenylacetylene (1.78 g, 10 mmol) as described for analogues **11c**, **12c**. According to the ^1H NMR spectrum, the orange oil obtained after hydrolysis of the tetrachloroaluminates **9d**, **10d** consisted of a 3:2 mixture of **11d** and **12d**. The products (2.22, 84%) were separated by column chromatography (125 g $SiO_2$for flash-chromatography, pentane/Et_2O (7:2) as eluent). A first fraction consisted of a mixture of compounds. From the second fraction compound, **11d** was obtained as pale yellow powder (0.62 g, 24%); m.p. 71–73°C (dec). ^1H NMR ($CDCl_3$): δ 1.43 (t, J = 7.2), 2.27 (CH_3), 4.11 (q, J = 7.2) (CH_2), 7.13–7.46 (m's, phenyl). ^{13}C-NMR ($CDCl_3$): δ 9.8, 15.4, 44.2 (CH_3, CH_2), 118.5, 126.4, 127.0, 127.9, 128.0, 128.3, 130.2, 133.8, 134.3, 136.3, 147.9 (phenyl, C=). Anal. calcd. for $C_{18}H_{18}N_2$ (262.4): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.34; H, 7.26; N, 9.60; MS: m/z (EI) 262.

A third fraction of the column chromatography afforded **12d** as orange oil (0.39 g, 14%). ^1H NMR ($CDCl_3$): δ 0.54 (t, J = 7.4), 1.95 (CH_3), 2.36 (m, CH_2), 7.08–7.67 (m's, 10 H, phenyl). ^{13}C NMR ($CDCl_3$): δ 7.6, 12.2, 24,6 (CH_3, CH_2), 72.8 (C4), 125.8, 127.6, 128.1, 128.6, 129.5, 130.8, 135.1 (phenyl), 176.9, 179.9 (C=N). Anal. calcd. for $C_{18}H_{18}N_2$ (262.4): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.58; H, 7.21; N, 10.28; MS: m/z (EI) 262.

3,3-Dimethyl-4,5-diphenyl-3H-Pyrazole (13)

From **6** ($R^1 = R^2 =$ Me)[42,43] (1.83 g, 10 mmol) and diphenylacetylene (1.78 g, 10 mmol) (method B). Hydrolysis of the brown oily tetrachloroaluminate **8** afforded an orange oil, which crystallized at −15°C from EtOH (15 ml) to furnish a pale yellow powder (1.80 g, 72%); m.p. 81–83°C (dec). ^1H-NMR ($CDCl_3$): δ 1.51 (6H, CH_3), 7.14–7.75 (m's, 10H, phenyl). ^{13}C-NMR ($CDCl_3$): δ 20.6 (CH_3), 96.7 (C), 127.7, 128.2, 128.4, 128.5, 129.1, 131.3, 133.3, 149.2, 152.0 (aryl, C=). Anal. calcd. for $C_{17}H_{16}N_2$ (248.3): C, 82.23; H, 6.49; N, 11.28. Found: C, 82.27; H, 6.46; N, 11.25; MS: m/z (EI) 248.

4,5-Dimethyl-3-phenyl-1H-Pyrazolium Perchlorate (15f)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and phenylacetylene (1.23 g, 12 mmol) (method B). From the black oily tetrachloroaluminate **14f** the perchlorate **15f** was obtained as colorless powder. Yield: 2.32 g (85%) m.p. 110–112°C (dec). ^1H NMR ($CDCl_3$): δ 2.16, 2.43 (6H, 2*CH3*); 7.61 (m, phenyl); 12.30 (br, NH). ^{13}C NMR ($CDCl_3$): δ 8.3, 10.1 (*CH3*); 115.4 (C4); 126.9, 129.4, 130.4, 132.0, 146.3, 146.7 (phenyl, C=). Anal. calcd. for $C_{11}H_{13}NClN_2O_4$ (272.3): C, 48.45; H, 4.81; N, 10.27. Found: C, 48.37; H, 4.89; N, 10.26; MS: m/z (EI) 272.

3-Butyl-4,5-dimethy-1H-Pyrazolium Picrate (15g)

From **6** (R^1= R ^{2}= Me) (1.83 g, 10 mmol) and 1-hexyne (0.99 g, 12 mmol) (method B). Hydrolysis afforded an orange oil, which was dissolved in EtOH (12 ml). A saturated solution of picric acid in EtOH (ca 30 ml) was added. At – 15°C crystallized as yellow powder (2.12 g, 76%); m.p. 122–124°C (dec). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.4, 3H), 1.25–1.64 (m, 4 H), 2.04, 2.41 (CH_3), 2.71 (t, J= 7.4, 2 H), 8.94 (br, NH). ^{13}C NMR ($CDCl_3$): δ 7.2, 9.8, 13.5, 22.7, 24.2, 30.3 (CH_3, CH_2), 113.7 (C4); 126.3, 129.5, 130.4, 141.1, 143.1, 147.3, 161.5 (aryl, C=). Anal. calcd. for $C_{15}H_{19}N_5O_7$ (381.1): C, 47.24; H, 5.02; N, 18.37. Found: C, 47.37; H, 4.89; N, 18.26; MS: m/z (EI) 381.

2,5-Dihydro-2,2-dimethyl-5-phenylimino-1,3,4-thiadiazole (19a)[44]

From **6** (R^1= R^2= Me) (1.83 g, 10 mmol) and phenyl isothiocyanate (1.35 g, 10 mmol). The orange oily hexachloroantimonate **18a** was precipitated from the reaction mixture by addition of pentane (120 ml). Hydrolysis afforded **19a** as a yellow powder, which was crystallized at −15°C from Et_2O (50 ml) to furnish a pale yellow powder. Yield: 1.50 g (73%) m.p. 100–102°C (lit.[44]] m.p. 100–102°C). ^{1}H NMR ($CDCl_3$): δ 1.86 (2 *CH3*); 7.24–7.48 (m, phenyl). ^{13}C NMR ($CDCl_3$): δ 28.3 (2C, 2*CH3*); 106.9 (C2); 121.0, 126.8, 129.4, 148.2 (phenyl); 174.3 (C=N). Anal. calcd. for $C_{10}H_{11}N_3S$ (205.3): C, 58.51; H, 5.40; N, 20.47. Found: C, 58.02; H, 5.46; N, 20.91; MS: m/z (EI) 205.

5-Benzlimino-2,5-dihydro-2,2-dimethyl-1,3,4-thiadiazol (19b)

From **6** (R^1= R^2= Me) (1.83 g, 10 mmol) and benzyl isothiocyanate (1.49 g, 10 mmol). The orange oil obtained after hydrolysis was crystallized at −15°C from Et_2O (50 ml) to furnish an orange semisolid powder. Yield: 1.40 g (64%) m.p. 39–41°C. ^{1}H NMR ($CDCl_3$): δ 1.85 (2*CH3*); 1.64 (2H,*CH2*); 7.25–7.45 (m, phenyl). ^{13}C NMR ($CDCl_3$): δ 28.4 (2C, 2 *CH3*); 62.3 (*CH2*) 106.4 (C2); 127.3, 127.9, 128.6, 137.8 (phenyl); 177.0 (C=N). Anal. calcd. for $C_{11}H_{13}N_3S$ (219.3): C, 60.24; H, 5.97; N, 19.16. Found: C, 60.14; H, 5.94; N, 19.00; MS: m/z (EI) 219.

1,3-Bis(2,5-dihydro-2,2-dimethyl-1,3,4-thiadiazol-5-ylideneamino)benzene (19c)

From **6** (R^1= R^2= Me) (3.66 g, 20 mmol), 1,3-phenylene diisothiocyanate (1.92 g, 10 mmol) and $SbCl_5$ (5.98 g, 20 mmol). The dark brown oily hexachloroantimonate was precipitate from the reaction mixture by addition of pentane (150 ml). Hydrolysis afforded **19c** as a yellow powder, which crystallized at -15°C from Et_2O (100 ml) to furnish a pale yellow powder. Yield: 2.56 g (77%) m.p. 124–126°C (dec). ^1H NMR ($CDCl_3$): δ 1.88 (12 H,*CH3*); 7.15–7.55 (m, phenyl). ^{13}C NMR ($CDCl_3$): δ 28.3 (4C, 4 *CH3*); 107.3 (2 C2); 113.1, 119.3, 130.4, 149.4 (phenyl); 175.1 (C=N). Anal. calcd. for $C_{14}H_{16}N_6S_6$ (332.4): C, 50.58; H, 4.85; N, 25.28. Found: C, 50.22; H, 4.84; N, 24.76; MS: m/z (EI) 332.

4,5-Dihydro-3,3-dimethyl-4-phenyl-3H-1,2,4-triazol-5-one (23a)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and phenyl isocyanate (1.19 g, 10 mmol). The brown powder obtained after hydrolysis was crystallized at −15°C from Et_2O (60 ml) to furnish a brown powder. Yield: 1.59 g (84%) m.p. 136–138°C (dec). ^1H-NMR ($CDCl_3$): δ 1.63 (6H, 2 *CH3*); 7.20–7.53 (m, phenyl). ^{13}C NMR ($CDCl_3$): δ 23.4 (*CH3*); 101.3 (C3); 126.7, 128.9, 130.0 (phenyl); 160.1 (C = O). Anal. calcd. for $C_{10}H_{11}N_3O$ (189.2): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.21; H, 5.93; N, 22.45; MS: m/z (EI) 189.

4,5-Dihydro-3,3-dimethyl-4-(4-methylphenyl)-3H-1,2,4-triazol-5-one (23b)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and p-tolyl isocyanate (1.33 g, 10 mmol). The resulting orange oil obtained after hydrolysis dissolved in Et_2O (140 ml). Filtration and evaporation of the solvent afforded a pale yellow powder, which was recrystallized at −15°C from Et_2O (50 ml) to furnish a pale yellow powder. Yield: 1.67 g (82%) m.p. 100–102°C (dec). ^1H NMR ($CDCl_3$): δ 1.60 (s, 2 *CH3*); 2.39 (3H, *CH3*); 7.05–7.30 (m, phenyl). ^{13}C NMR ($CDCl_3$): δ 21.1, 23.3 (2C, 2*CH3*); 101.2 (C3); 126.6, 130.6, 139.1 (phenyl); 160.1 (C=O). Anal. calcd. for $C_{11}H_{13}N_3O$ (203.2): C, 65.01; H, 6.45; N, 20.68. Found: C, 65.23; H, 6.51; N, 21.30; MS: m/z (EI) 203.

4,5-Dihydro-3,3-dimethyl-4-(2-tricycl[3.3.1^{3,7}]decyl)-3H-1,2,4-triazol-5-one (23c)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and 2-adamantyl isocyanate (1.77 g, 10 mmol). The resulting colorless powder obtained after hydrolysis was crystallized powder at −15°C from $CHCl_3$ (20 ml) / pentane (7 ml) to furnish a colorless powder. Yield: 1.65 g (63%) m.p. sublimation above 158°C. ^1H NMR ($CDCl_3$): δ 1.59 (s, 2 *CH3*); 1.65–2.30 (m, 12H); 2.53 (br, 2H,*CH2*); 2.58 (br, 1H,*CH*). ^{13}C NMR ($CDCl_3$): δ 23.2 (2C, 2*CH3*); 27.2, 31.4, 32.3, 27.3, 38.3, 61.7 (*CH2*, *CH*); 102.1 (C3);

161.5 (C = O). Anal. calcd. for $C_{14}H_{21}N_3O$ (247.3): C, 67.99; H, 8.56; N, 16.99. Found: C, 68.05; H, 8.71; N, 17.410; MS: m/z (EI) 247.

4,5-Dihydro-3,3-dimethyl-4-phenyl-5-phenylimino-3H-1,2,4-triazole (27a)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and diphenyl carbodiimide (1.94 g, 10 mmol).[49] The orange powder obtained after hydrolysis was dissolved in pentane (100 ml). Filtration from an impurity, evaporation of the solvent and crystallization of the residue at −15°C from Et_2O (30 ml) afforded orange prisms. Yield: 1.90 g (72%) m.p. 86–88°C (dec). ^{1}H-NMR ($CDCl_3$): ca (5:1) mixture of two isomers; major component δ 1.62 (6H, *2 CH3*); 7.01–7.49 (m, phenyl); minor component δ 1.56 (very br, 6H, *2 CH3*); 6.63–7.01 (very br, phenyl). ^{13}C-NMR ($CDCl_3$): major component δ 22.2 (2 *CH3*); 102.7 (C3); 123.5, 123.7, 126.9, 127.6, 128.5, 129.7, 135.8, 147.3 (phenyl); 156.2 (C=N); minor component δ 24.4 (very br), 105.6 (very br, C3). Anal. calcd. for $C_{16}H_{16}N_4$ (264.3): C, 72.70; H, 6.10; N, 21.20. Found: C, 72.82; H, 6.31; N, 21.52; MS: m/z (EI) 264.

4,5-Dihydro-4-isopropyl-3,3-dimethyl-5-phenylimino-3H-1,2,4-triazole (27b)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and isopropylphenylcarbodiimide (1.60 g, 10 mmol).[50] The orange oil obtained after hydrolysis was dissolved in Et_2O (150 ml). Filtration from an impurity, evaporation of the solvent and crystallization of the residue at −15°C from pentane (35 ml) afforded an orange powder. Yield: 1.57 g (68%) m.p. 57–59°C (dec). ^{1}H NMR ($CDCl_3$): δ 1.47 (d, 6H, J= 6.9, 2*CH3*); 1.55(6H, 2*CH3*); 3.84(sept, 1H,*CH*); 7.01–7.33 (m, phenyl). ^{13}C NMR ($CDCl_3$): δ 19.3, 23.4 (2C, 2 *CH3*); 45.2 (*CH*); 102.0 (C3); 122.8, 123.8, 128.6, 148.1 (phenyl); 154.7 (C=N). Anal. calcd. for $C_{13}H_{18}N_4$ (230.3): C, 67.80; H, 7.88; N, 24.33. Found: C, 67.84; H, 8.01; N, 24.20; MS: m/z (EI) 230.

4-Cyclohexyl-5-cyclohexylimino-4.5-dihydro-3,3-dimethyl-3H-1,2,4-triazole (27c)

From **6** ($R^1 = R^2 =$ Me) (1.83 g, 10 mmol) and dicyclohexylcarbodiimide (2.06 g, 10 mmol). The orange oily hexachloroantimonate **26** was precipitated from the reaction mixture by addition of pentane (100 ml). Hydrolysis afforded **27c** as a yellow powder, which was dissolved in Et_2O (150 ml). Filtration from an impurity, evaporation of the solvent and crystallization of the residue at −15°C from Et_2O (150 ml) afforded a yellow powder. Yield: 1.85 g (67%) m.p. 95–97°C (dec). ^{1}H NMR ($CDCl_3$):

δ 1.47 (6H, 2*CH3*);1.13–1.83 (m, 9*CH2*); 2.17 (m, 2H,*CH2*); 3.26 (br,*CH*); 4.49 (br,*CH*). ^{13}C NMR (CDCl$_3$): δ 24.0, 24,8, 25.4, 26.0, 26.2, 29.1, 35.9 (br, *CH3*, *CH2)*; 53.0, 56.6 (br,*CH*); 100.4 (br, C3); 156.1 (C=N). Anal. calcd. for $C_{16}H_{28}N_4$ (267.4): C, 69.52; H, 10.21; N, 20.27. Found: C, 69.26; H, 10.16; N, 19.97; MS: m/z (EI) 267.

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