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Cycloaddition reactions of 1,3-diazabuta-1,3-dienes with alkynyl ketenes

Giorgio Abbiati *, Alessandro Contini, Donatella Nava, Elisabetta Rossi

DISMAB—Sezione Chimica Organica 'Alessandro Marchesini', Università degli Studi di Milano, Via Venezian 21, I-20133 Milano, Italy

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ABSTRACT

The cycloaddition reactions of 'all-carbon' 1,3-diazabuta-1,3-dienes with a few conjugated and unconjugated alkynyl ketenes are described. The reactions provide some interesting azetidinones and dihydropyrimidinones bearing an alkynyl moiety. The regiochemistry of cycloadduct is related with the degree of conjugation of the alkynyl ketene. Moreover, two alternative approaches to 'all-carbon' 1,3-diazabuta-1,3-dienes are reported.

1. Introduction

Cycloaddition reactions involving 1,3-diazabuta-1,3-dienes represent a useful strategy for the preparation of a number of four-, five- and six-member nitrogen-containing heterocycles.[1] A wide variety of different reaction partners were tested and a lot of example of cycloaddition reactions with different partners, such as isocyanides,[2] phosphoric compounds,[3] the Simmons–Smith reagent,[4] acetylenes,[5] enamines,[6] sulfenes,[7] oxazolinones,[8] acrylates,[9] the Reformatsky reagent,[10] nitriles[11] and α-nitrostyrenes,[12] have been reported. However, cycloaddition reactions between differently substituted 1,3-diazabuta-1,3-dienes and ketenes represent the most studied application of these compounds in heterocyclic synthesis, leading up to several different azetidinones and pyrimidinones.[5,13] In connection with our ongoing interest in the synthesis of heterocyclic compounds starting from amidines and their derivatives,[14] we widely investigated the cycloaddition reactions of a few 2,4-diphenyl-1,3-diazabuta-1,3-dienes characterised by (1) the mono-substitution on C-4 and (2) the 'all-carbon' substitution on the diazadiene scaffold. We explored the reactivity of these substrates with mono and di-substituted ketenes[15] and the thermal and photochemical cycloreversion of the [2+2] cycloadduct into the corresponding [4+2] adduct.[16] We extended our study to the cycloaddition reactions with some chiral ketenes leading up to optically active azetidinones.[17] Furthermore, we investigated the cycloaddition reactions with isocyanates and isothiocyanates to give triazin-2-ones and triazin-2-thiones.[18]

The aim of this work is to conclude our investigation on the cycloaddition between 1,3-diazabuta-1,3-dienes and ketenes testing the reactivity of some unusual alkynyl ketenes. To our knowledge, this feature of the chemistry of 1,3-diazabuta-1,3-dienes was never previously investigated and only a few researchers have explored the reactivity of some alkynyl ketenes with imines.[19–22] For example, in a more extensive study on the reactivity of cyanoketenes with imines,[19] Moore and Nguyen investigated the cycloaddition of cinnamylideneamines and benzylideneamines with the strongly activate hexynylcyanoketene, generated in situ by the thermolysis of 2,5-diazido-3,6-dihexynyl-1,4-benzoquinone.[20] Alcaide and co-workers reported the first example of a cycloaddition of a diimine with an unconjugated alkynyl ketene generated in situ from the corresponding acyl chloride.[21] More recently, Rosenblum and co-workers prepared some 3-alkynyl azetidinones in low to moderate yields, through the cycloaddition of aryl alkynyl ketenes and (4-methoxy-benzylidene)-phenyl-amine.[22] In this paper we report two new favourable strategies to prepare 'all-carbon' 1,3-diazabuta-1,3-dienes and the results of our experimental studies on their cycloaddition reactions with simple acetylenic ketenes.

2. Results and discussion

Some years ago, we described a new useful synthetic approach to the 1,3-diazabuta-1,3-diene framework starting from dibutylphosphoramidates and aryl aldehydes.[14b] Despite the method working well for the preparation of *N*-aryl diazadienes, the overall

* Corresponding author. Tel.: +39 02 50314474; fax: +39 02 50314476.
E-mail address: giorgio.abbiati@unimi.it (G. Abbiati).

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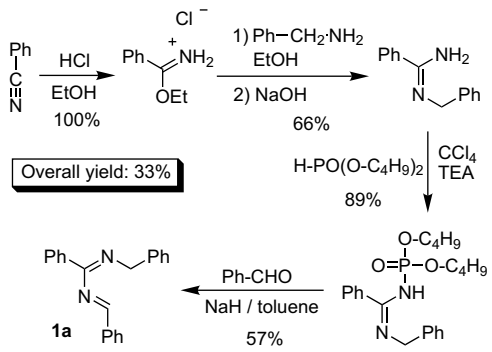
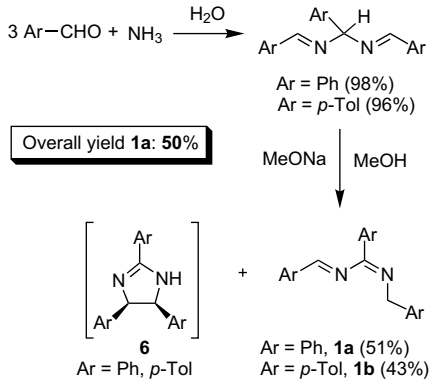


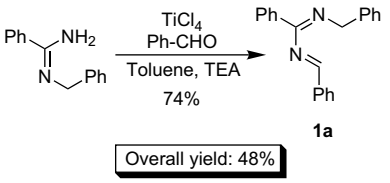
Scheme 1.

yield for the synthesis of the 1-benzyl-2,4-diphenyl-1,3-diazabuta-1,3-diene **1a**[15] was improvable (Scheme 1).

An alternative approach was developed through the optimisation of a method previously reported by Hunter and Sim.[23] The synthesis of diazadiene **1a** was achieved in 51% yield by a base-promoted prototropic rearrangement of the corresponding hydrobenzamide (Scheme 2).[24] The latter was easily obtained in almost quantitative yield through the condensation of benzaldehyde with concentrated aqueous ammonia. Although a significant amount of the by-product amarine **6** was obtained besides the desired product **1a**, the number of steps, the cheapness of reagents, the easy product isolation and the overall process yields (50%) made this synthetic strategy useful (Scheme 2). Moreover, this method was successfully used to prepare the new diazadiene **1b** in 43% yield



Scheme 2.



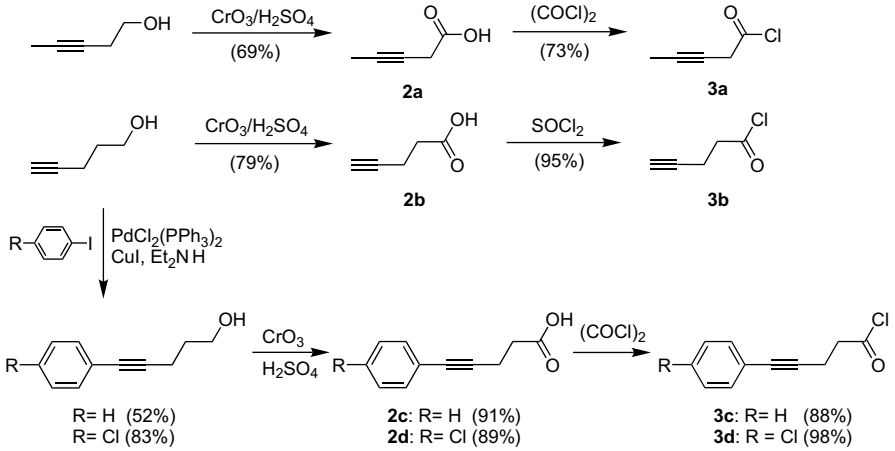
Scheme 3.

starting from *p*-tolyl-benzaldehyde (Scheme 2). Clearly, the drawback of this approach is to allow only the synthesis of homo-substituted 2,4-diaza-1,3-pentadienes.

An alternative synthesis was developed on the basis of Würthwein's findings.[25] It is well known that titanium tetrachloride can promote imine intermediate formation through its vigorous water scavenger and useful Lewis acid double activity.[26] Thus, **1a** was prepared by direct condensation of *N*-benzyl benzamidine with benzaldehyde in the presence of half equivalent of $TiCl_4$ in toluene and an excess of triethylamine (Scheme 3). The greatest strength of this approach is the ease of product isolation. With respect to the standard method the overall process yield was increased to 48%.

Regarding the dienophile reaction partner, alkynyl ketenes were generated in situ by dehydrohalogenation of the corresponding acyl chlorides **3a**–**d**. The latter were easily prepared in good yields according to the standard methods by reacting the corresponding acids **2a**–**d** with thionyl chloride or oxalyl chloride. Alkynoic acids **2a**–**d** were synthesised in good yields starting from the corresponding alkynols by an 'inverse addition' Jones oxidation.[27] Finally, 5-aryl-4-pentyn-1-ols **2c**,**d** were obtained by means of Sonogashira coupling[28] of 4-pentynol with the appropriate aryl iodide[29] (Scheme 4).

Cycloaddition reactions of diazadienes **1a**,**b** and alkynyl ketenes were initially performed following the standard procedure reported in our previous works[15] (method A), by slow addition of a solution of the appropriate acyl chloride (1.1 mmol) in dry toluene to an ice cooled diluted solution (about 0.085 M) of 1,3-diaza-1,3-diene (1 mmol) and triethylamine (2.3 mmol) in dry toluene. Unexpectedly, under these conditions the reactions failed or gave very poor yields (Scheme 5). It has been reported that reaction between an acid halide and an imine in the presence of triethylamine to give the azetidinone nuclei only works well if the acid halide have an electron-withdrawing substituent in the α-position.[30a] On the other hand, it has been demonstrated that a suitable choice of the reaction conditions (solvent, base, temperature, concentration) can affect both the yields and the stereoselectivity of the cycloaddition

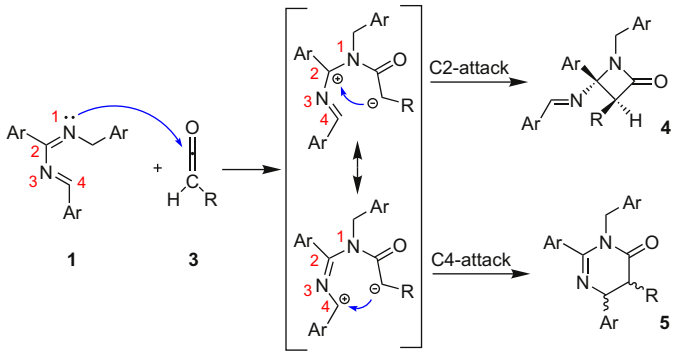


Scheme 4.

reactions involving base-generated ketenes.[30b] Thus, better results were obtained by optimising the reaction conditions suggested by Vaccaro[30b] for inactivated ketenes (method B), i.e., by slow addition of a solution of the acyl chloride (1.5 mmol) in dry toluene to a well stirred solution of 1,3-diaza-1,3-butadiene (1 mmol) and tributylamine (2.5 mmol) in dry toluene at rt under a nitrogen atmosphere, as reported in Scheme 5.

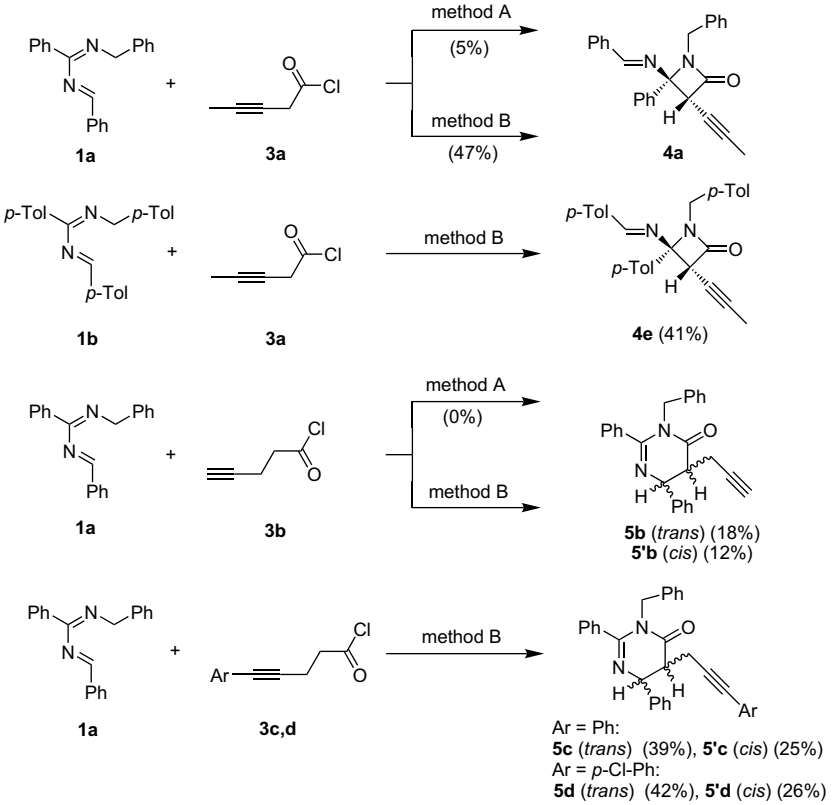
The reaction of the conjugated alkynyl ketene, obtained in situ by slow addition of **3a** to a toluene solution of **1a** in the presence of 2.5 equiv of tributylamine at rt (method B), gave the desired azetidinone **4a** in moderate yields. The regiochemical preference of reactions performed in the presence of conjugated alkynyl ketenes was confirmed by the results of the cycloaddition reactions with diazadiene **1b**. As previously reported,[16] the diastereoselectivity of this [2+2] cycloaddition was demonstrated by ^{1}H NMR spectroscopic analysis and NOE experiments showing the presence of a single diastereoisomer with a cis relationship between the benzylideneimino group at C-4 and the hydrogen on C-3. Unexpectedly, unconjugated ketenes derived from acyl chlorides **3b**–**d** showed different behaviour. Under standard conditions (method A), the reaction of **1a** with the ketene derived from **3b** failed, giving rise to a complex mixture of unidentified products besides traces of 1-benzyl-2,4,6-triphenyl-1,2-dihydro-[1,3,5]triazine.[31] On the contrary, the reaction performed under the new conditions (method B) resulted in a diastereoisomeric mixture of dihydropyrimidinones **5b**(*trans*) and **5′b**(*cis*) in 3:2 ratio. Despite the unsatisfactory reaction yield, no trace of azetidinone **4b** was detected by TLC in the reaction crude. Moreover, an identical regio- and stereochemical outcome, but in better yield, was observed by reacting **1a** with ketenes arising from acyl chloride **3c**,**d**.

As reported in the literature,[5,13c,e] the most widely accepted mechanism for the cycloaddition reactions of 1,3-diaza-1,3-dienes and ketenes involves the nucleophilic attack of N-1 of the diene upon the carbonyl group of ketene, thus leading to the formation of a zwitterionic intermediate. Subsequent intramolecular attack of the nucleophilic α-C of carbonyl group on C-2 or C-4 of the diene system can lead to the formation of β-lactams or dihydropyrimidinones, respectively (Scheme 6).



Scheme 6.

Mahajan and co-workers[32] have also recently published the results of ab initio calculations performed on the [2+2] cycloaddition reaction between the unsubstituted 1,3-diazabuta-1,3-diene and ketene that confirm the intermediacy of a zwitterionic compound. Moreover, these results are in concordance with the ab initio study on the mechanism of imine–ketene cycloaddition (Staudinger reaction) reported by Sordo,[33] which confirmed the experimental data obtained by Moore and co-workers.[19] Finally, Chemouri and Mekelleche recently reported a theoretical study dealing with the mechanism and the regiochemistry of the cycloaddition of 1,3-diazabuta-1,3-dienes with ketenes using DFT-based reactivity indexes.[34]



Method A: **1**/**3**/TEA = 1:1.1:2.3, toluene, from 0 °C to rt
Method B: **1**/**3**/TBA = 1:1.5:2.5, toluene, rt.

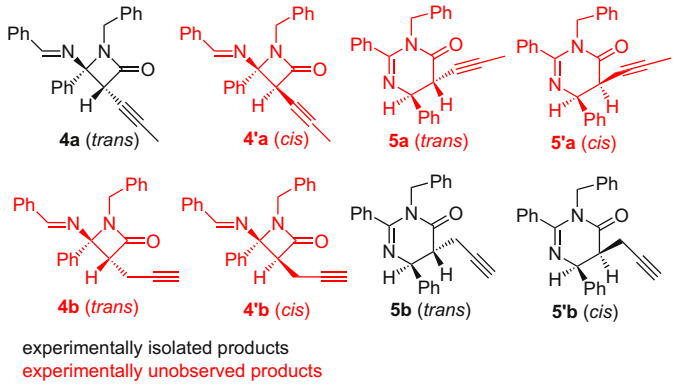
Scheme 5.

With the aim to clarify the different outcome observed by reacting conjugated versus unconjugated ketenes, the problem was tentatively approached from a theoretical point of view. The investigation was restricted to all potential products arising from the [2+2] and [4+2] cycloaddition reaction of diazadiene **1a** with alkynyl ketenes derived from **3a** and **3b**. We calculated the minima energies of geometric isomers of azetidinones **4a**,**b**/**4′a**,**b** and dihydropyrimidinones **5a**,**b**/**5′a**,**b** at ground state. The minimisations were performed at the DFT level using the B3LYP functional and the 6-31+G(d,p) basis-set.[35] Calculations were performed on isolated molecules in the gas phase and the character of minima was confirmed by the absence of imaginary frequencies. Selected ΔE among isolated and hypothetical isomers are reported in Table 1.

The energetic difference between trans and cis form of both azetidinones **4a**/**4′a** and **4b**/**4′b** was very low (0.1 and 0.4 kcal/mol, respectively, in favour of product cis), according to the statement that configurational preferences in such cycloaddition are controlled by orbital symmetry and torquoselectivity considerations[36] rather than relative stability of isomeric products (entries 1 and 2). The not isolated cis isomer **5′a** was slightly favoured over the trans isomer **5a** ($\Delta E_{cis-trans}=-0.7$ kcal/mol), while an opposite relationship was observed for the couple **5b**/**5′b** (derived from the reaction with the unconjugated ketenes) where the trans isomer **5b** was 1 kcal/mol more stable than **5′b**, in concordance with the ratio trans/cis=3:2 experimentally observed (see Scheme 5). Finally, no substantial differences were observed among the ΔE between the more stable isomeric forms of the couples azetidinone/dihydropyrimidinone **4′a**/**5a** and **4′b**/**5b**: in both cases, the calculated ΔE were high, confirming that azetidinones can only arise under kinetic control whereas dihydropyrimidinones are the thermodynamic products.

Despite these computational results providing insights into the reaction thermodynamics, they were unable to explain the regiochemical behaviour observed and probably only an in-depth theoretical investigation on the transition states involved could clarify the relationship between specificity observed and the degree of conjugation of the ketene, but this is beyond the scope of this paper. A simple comparison between the structures of the two possible zwitterions shows that the intermediate derived from the reaction of azadiene **1a** with the ketene **3a** could be stabilised by the presence of a conjugated π-system on the ketene moiety capable of delocalising the negative charge. As already reported,[15] this would theoretically increase the tendency to give the thermodynamically controlled cycloadduct. On contrary, we observed an opposite experimental behaviour. These evidences suggest that the regiochemical outcome is not controlled by simple and intuitive electronic factors. Probably the mode of cyclisation is determined by steric reasons and/or some kind of specific π-interaction between the different alkynyl moieties and the benzylidene framework in the zwitterionic intermediates.

Table 1
Selected ΔE (kcal/mol) among isolated and hypothetical isomers



Entry	Compounds	ΔE^a
1	**4′a**(*cis*)–**4a**(*trans*)	−0.1
2	**4′b**(*cis*)–**4b**(*trans*)	−0.4
3	**5′a**(*cis*)–**5a**(*trans*)	−0.7
4	**5′b**(*cis*)–**5b**(*trans*)	1.0
5	**4′a**(*cis*)–**5a**(*trans*)	13.7
6	**4′b**(*cis*)–**5b**(*trans*)	20.0

[a] ZPE corrected energy differences.

3. Conclusions

In conclusion, two alternative approaches to 'all-carbon' 1,3-diazabuta-1,3-dienes have been reported. Some examples of regiospecific cycloaddition reactions of these substrates with conjugated and unconjugated alkynyl ketenes have been presented. These reactions gave rise in modest to good yields to some interesting azetidinones and dihydropyrimidinones bearing an alkynyl moiety susceptible to further modification.

4. Experimental

4.1. General details

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Fluka silica gel F_{254} thin-layer plates were employed for thin-layer chromatography (TLC). Davisil silica gel LC 60A was employed for flash column chromatography. Melting points, measured with a Stuart Scientific SMP3 apparatus, are uncorrected. Infrared spectra were recorded on an FT-IR Perkin Elmer Spectrum One spectrophotometer using KBr tablets. Proton NMR spectra were recorded at rt in $CDCl_3$, on Varian-Gemini 200 at 200 MHz, with residual chloroform as the internal reference (δ_H=7.27 ppm). ^{13}C NMR spectra were recorded at rt in $CDCl_3$, on the same spectrometer, at 50.3 MHz, with the central peak of chloroform as the internal reference (δ_C=77.3 ppm). The APT or DEPT sequences were used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. Two-dimensional NMR experiments (NOESY) were used, where appropriate, to aid in the assignment of signals in the proton spectra. 'PE' refers to the fraction of petroleum ether with boiling point of 40–60 °C. 'EtOAc' means ethyl acetate. TEA means triethylamine. 1,3,5-Triaryl-2,4-diaza-1,4-pentadienes[23,24] (hydrobenzamides), diazadiene **1a**,[15,23] 3-pentynoic acid,[35] 4-pentynoic acid,[27] 3-pentynoic acyl chloride,[37] 4-pentynoic acyl chloride,[38] 5-phenyl-4-pentyn-1-ol,[29] 5-phenyl-4-pentynoic acid[22] and 5-phenyl-4-pentynoic acyl chloride[22] are known compounds.

4.2. Synthesis of hydrobenzamides

A mixture of benzaldehyde or 4-methyl-benzaldehyde (83.0 mmol) and aqueous ammonia 30% (60.0 mL) was stirred for 3 days at rt. The white solid is filtered over a Buchner funnel and dried under vacuum over $CaCl_2$.

4.2.1. 1,3,5-Triphenyl-2,4-diaza-1,4-pentadiene
Yield 8.09 g, 98%. White solid.

4.2.2. 1,3,5-Tri-(4-methyl-phenyl)-2,4-diaza-1,4-pentadiene
Yield 9.04 g, 96%. White solid.

4.3. Base-promoted prototropic rearrangement of the hydrobenzamides

The appropriate hydrobenzamide (7 mmol) was stirred for 3 days at 40 °C in 0.5 M sodium methoxide/methanol (20 mL). The

solvent was quickly removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with NaH_2PO_4 (2×20 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent removed at reduced pressure. To completely remove the by-product (amarine), the residue was purified through a rapid flash chromatography over a short silica gel column (eluent: PE/TEA=8:2).

4.3.1. N-Benzyl-N′-benzylidene-benzamidine ***1a***

Yield 1.06 g, 51%. White-yellowish solid. Mp: 87–90 °C (lit.[15] 89–90 °C).

4.3.2. 4-Methyl-N-(4-methyl-benzyl)-N′-(4-methyl-benzylidene)-benzamidine ***1b***

Yield 1.02 g, 43%. White solid. Mp: 67–68 °C. IR (KBr) ν=1637, 1605 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 7.12–7.38 (m, 8H, arom.), 7.76–7.83 (m, 4H, arom.), 8.15 (s, 1H, CH=N) ppm. ^{13}C NMR: δ=21.4, 21.6, 21.9 (CH_3), 53.1 (CH_2), 127.9, 128.0, 129.1, 129.2, 129.9 (CH arom., one signal obscured), 132.7, 133.5, 136.0, 138.6, 140.6, 143.3 (C quat. arom.), 161.9 (CH=N), 164.2 (N–C=N) ppm. $C_{24}H_{24}N_2$ (340.46): calcd C 84.67, H 7.11, N 8.23; found: C 84.58, H 7.05, N 8.28.

4.4. $TiCl_4$ promoted synthesis of 1a

To a stirred solution of *N*-benzyl benzamidine (2.0 g, 9.5 mmol), benzaldehyde (1.1 g, 10.4 mmol) and triethylamine (2.4 g, 23.8 mmol) in dry toluene (56 mL) at 0 °C, a solution of $TiCl_4$ (0.90 g, 4.8 mmol) in dry toluene (18 mL) was slowly added (90 min) dropwise under a nitrogen atmosphere. After that the mixture was stirred for additional 5 h at rt. The resulting white-yellow suspension was rapidly filtered under vacuum over a Celite pad and the clear liquid was stored in a sealed flask overnight at 4–6 °C. The cold cloudy solution was re-filtered under vacuum over a well-pressed Celite pad and freed from solvent under reduced pressure without heating to give **1a**. Yield: 2.1 g, 74%. White solid, mp 88–90 °C.

4.5. Synthesis of 5-aryl-4-pentyn-1-ols

Under a nitrogen atmosphere, a solution of 4-pentyn-1-ol (2.0 g, 23.8 mmol), the appropriate aryl-halide (23.8 mmol), CuI (23 mg, 0.12 mmol) and $PdCl_2(PPh_3)_2$ (170 mg, 0.24 mmol) in dry diethylamine (40 mL) was stirred overnight at rt, until no more starting product was detectable by TLC analysis. The excess diethylamine was removed under reduced pressure, the residue diluted with brine (150 mL) and extracted with EtOAc (3×40 mL). The organic layer, dried over anhydrous sodium sulfate, was evaporated to dryness and the crude purified by flash chromatography over a silica gel column (eluent: PE/EtOAc=8:2).

4.5.1. 5-(4-Chlorophenyl)-4-pentyn-1-ol

Yield 3.71 g, 83%. Yellow oil. IR (NaCl) ν=3339 (O–H), 2234 (C≡C), 1489 (C=C), 1060 (C−OH) cm^{-1}. ^1H NMR: δ=1.61 (br s, 1H, OH), 1.88 (quin., 2H, CH_2–*CH_2* CH_2–OH, J=6.6 Hz), 2.55 (t, 2H, *CH_2*–CH_2CH_2–OH, J=6.6 Hz), 3.84 (t, 2H, CH_2–CH_2*CH_2*–OH, J=6.5 Hz), 7.30 (m, 4H, arom.) ppm. ^{13}C NMR: δ=16.2, 31.5, 61.7 (CH_2), 80.3, 90.7 (C≡C), 128.7, 133.0 (CH arom.), 122.5, 133.8 (C quat. arom.) ppm.

4.6. General method for the oxidation of alcohols

A solution of the appropriate alcohol (15 mmol) in acetone (50 mL) was added dropwise (2 h) to a cooled solution of Cr_2O_3 (3.0 g, 30 mmol) in 10 M H_2SO_4 (37.5 mL), maintaining a temperature of 5–10 °C. The reaction mixture was stirred for additional 2 h at rt. After concentration under reduced pressure, the residue was dissolved in water (100 mL) and extracted with diethyl ether (4×50 mL). The combined organic layers were washed with water (50 mL) and the volume was reduced by half under reduced pressure. Then, the ether solution was extracted with 3 M NaOH (2×50 mL). The combined basic solution was cooled and acidified by dropping 37% HCl. The acidic solution was finally extracted with diethyl ether (3×50 mL). The organic layer, dried over sodium sulfate, was evaporated to dryness to give yellowish oil. The acids were sufficiently pure to be transformed into the corresponding acyl chlorides by standard methods without further purification.

4.6.1. 5-(4-Chlorophenyl)-4-pentynoic acid ***2d***

Yield 89%. Yellow oil. IR (NaCl) ν=3435 (O–H), 1694 (C=O), 1093 (C–Cl) cm^{-1}. ^1H NMR: δ=2.73 (m, 4H, CH_2–CH_2), 7.31 (m, 4H, *arom*), 10.50 (br s, 1H, COOH, exchange with D_2O) ppm. ^{13}C NMR: δ=15.3, 33.6 (CH_2), 80.6, 88.8 (C≡C), 122.1, 134.1 (C quat. arom.), 128.8, 133.1 (CH arom.), 178.6 (C=O) ppm. ESI-MS m/z (%): 209 [M^++1] (100).

4.6.2. 5-(4-Chlorophenyl)-4-pentynoyl chloride ***3d***

Yield 98%. Light-brown solid. ^1H NMR: δ=2.80 (t, 2H, CH_2, J=7.2 Hz), 3.22 (t, 2H, CH_2, J=7.2 Hz), 7.28, 7.34 (AA′BB′ system, 4H, arom. J=9.2 Hz) ppm.

4.7. Reactions of 1,3-diaza-1,3-butadienes 1a,b with ketenes 3a–d

4.7.1. Method A

A solution of the appropriate acyl chloride (1.1 mmol) in dry toluene (8 mL) was slowly added (1 h) to a nitrogen flushed, well stirred and ice-water cooled solution of 1,3-diaza-1,3-butadiene **1a** or **1b** (1.0 mmol) and triethylamine (2.3 mmol) in dry toluene (14 mL). After complete addition of the acyl chloride, the reaction mixture was stirred at 25 °C until no starting material was detected by TLC analysis. It was then washed with a cold saturated solution of $NaHCO_3$ (1×70 mL) and cold water (1×70 mL). The organic layer was dried over anhydrous sodium sulfate and freed from solvent under reduced pressure at 40 °C. The crude product was purified by flash chromatography over silica gel column.

4.7.2. Method B

A solution of the appropriate acyl chloride (1.5 mmol) in dry toluene (8 mL) was slowly added (1 h) to a nitrogen flushed, well stirred solution of 1,3-diaza-1,3-butadiene **1a** or **1b** (1.0 mmol) and tributylamine (2.5 mmol) in dry toluene (20 mL) at rt. After complete addition of the acyl chloride, the reaction mixture was stirred until no starting material was detected by TLC analysis. The reaction mixture was washed with 1 M HCl (1×70 mL) and 2 N NH_4Cl (1×70 mL). The organic layer was dried over anhydrous sodium sulfate and freed from solvent under reduced pressure at 40 °C. The crude product was purified by flash chromatography over silica gel column.

4.7.3. 1-Benzyl-4-(benzylidene-amino)-4-phenyl-3-prop-1-ynyl-azetidin-2-one ***4a***

Eluent for chromatography: PE/EtOAc (95:5). Orange oil. IR (KBr) ν=1765 (C=O), 1647 (C=C/C=N) cm^{-1}. ^1H NMR: δ=1.62 (d, 3H, CH_3, ^5J=2.7 Hz), 3.83 (d, 1H, CH_2, ^2J=15.0 Hz), 3.96 (q, 1H, C3H, ^5J=2.7 Hz), 4.84 (d, 1H, CH_2, ^2J=15.0 Hz), 7.26–7.64 (m, 15H, arom.), 7.95 (s, 1H, CH=N) ppm. ^{13}C NMR: δ=3.9 (CH_3), 45.5 (CH_2), 58.5 (C3–H), 70.4 (C4), 86.3, 86.4 (C≡C), 128.0, 128.2, 128.5, 128.6, 128.8, 128.9, 129.0, 129.5, 131.8 (CH arom.), 135.4, 136.5, 137.0 (C quat. arom.), 159.3 (CH=N), 165.6 (C=O) ppm. ESI-MS m/z (%): 379 [M^++1] (100). $C_{26}H_{22}N_2O$ (378.47): calcd C 82.51, H 5.86, N 7.40; found: C 82.42, H 5.84, N 7.38.

4.7.4. 1-(4-Methyl-benzyl)-4-[(4-methyl-benzylidene)-amino]-3-prop-1-ynyl-4-(4-methyl-phenyl)-azetidin-2-one ***4e***

Eluent for chromatography: PE/TEA (98:2).Yellow oil. IR (KBr) ν=1766 (C=O), 1645 (C=C/C=N) cm^{-1}. ^1H NMR: δ=1.63 (d, 3H, C≡C–CH_3, ^5J=2.7 Hz), 2.32 (s, 3H, CH_3), 2.38(s, 3H, CH_3), 2.39(s, 3H, CH_3), 3.77 (d, 1H, CH_2, ^2J=14.6 Hz), 3.92 (q, 1H, C3H, ^5J=2.7 Hz), 4.77 (d, 1H, CH_2, ^2J=14.6 Hz), 7.06–7.27 (m, 8H, arom.), 7.42 (m, 4H, arom.), 7.85 (s, 1H, CH=N) ppm. ^{13}C NMR: δ=4.0 (C≡C–CH_3), 21.3, 21.4, 21.7 (CH_3), 45.1 (CH_2), 58.3 (C3–H), 70.7 (C4), 80.0, 80.2 (C≡C), 128.5, 128.9, 129.2, 129.4, 129.5, 129.6 (CH arom.), 132.9, 133.6, 133.7, 137.6, 138.4, 142.1 (C quat. arom.) 159.0 (CH=N), 165.6 (C=O) ppm. $C_{29}H_{28}N_2O$ (420.55): calcd C 82.82, H 6.71, N 6.66; found C 82.59, H 6.74, N 6.61.

4.7.5. (trans)-3-Benzyl-2,6-diphenyl-5-prop-2-ynyl-5,6-dihydro-3H-pyrimidin-4-one ***5b****(trans)*

Eluent for chromatography: PE/TEA (95:5).Yellow oil. IR (KBr) ν=1698 (C=O), 1647 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.04–2.20 (m, 2H, C≡C–H and CH_2–C≡C), 2.79–2.94 (m, 2H, C5–H and CH_2–C≡C), 4.52 (d, 1H, Ph–CH_2, ^2J=15.4 Hz), 4.89 (d, 1H, C6–H, ^3J=11.7 Hz), 5.29 (d, 1H, Ph–CH_2, ^2J=15.4 Hz), 6.89 (m, 2H, arom.), 7.17–7.49 (m, 13H, arom) ppm. ^{13}C NMR: δ=17.4 (CH_2–C≡C), 45.5 (C5–H), 47.4 (Ph–CH_2), 61.2 (C6–H), 70.7 (C≡*C*–H), 80.9 (*C*≡C–H), 127.6, 127.7, 127.8, 127.9, 128.4, 128.6, 128.7, 128.9, 130.3 (CH arom.), 134.9, 137.2, 140.8 (C quat. arom.), 156.4 (CH=N), 170.8 (C=O) ppm. $C_{26}H_{22}N_2O$ (378.47): calcd C 82.51, H 5.86, N 7.40; found C 82.65, H 5.89, N 7.37.

4.7.6. (cis)-3-Benzyl-2,6-diphenyl-5-prop-2-ynyl-5,6-dihydro-3H-pyrimidin-4-one ***5′b****(cis)*

Eluent for chromatography: PE/TEA (95:5). Yellow oil. IR (KBr) ν=1698 (C=O), 1639 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.05–2.18 (m, 2H, C≡C–H and CH_2–C≡C), 2.62–2.84 (m, 1H, CH_2–C≡C), 3.20 (dt, 1H, C5–H, ^3J=8.4, 6.2 Hz), 4.86 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 4.96 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 5.24 (1H, C6–H, ^3J=6.2 Hz), 6.92 (m, 2H, arom.), 7.15–7.66 (m, 13H, arom) ppm. ^{13}C NMR: δ=15.4 (CH_2–C≡C), 44.7 (C5–H), 47.6 (Ph–CH_2), 60.1 (C6–H), 70.9 (C≡*C*–H), 81.4 (*C*≡C–H), 127.8, 127.9, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 130.4 (CH arom.), 135.1, 136.3, 136.8 (C quat. arom.), 156.9 (CH=N), 170.9 (C=O) ppm. $C_{26}H_{22}N_2O$ (378.47): calcd C 82.51, H 5.86, N 7.40; found C 82.49, H 5.84, N 7.41.

4.7.7. (trans)-3-Benzyl-2,6-diphenyl-5-(3-phenyl-prop-2-ynyl)-5,6-dihydro-3H-pyrimidin-4-one ***5c****(trans)*

Eluent for chromatography: PE/TEA (9:1).Yellow solid. Pf 141–143 °C. IR (KBr) ν=1690 (C=O), 1635 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.39 (dd, 1H, CH_2–C≡C, ^2J=16.5 Hz, ^3J=4.4 Hz), 2.93 (dt, 1H, C5–H, ^3J=4.4, 12.1 Hz), 3.18 (dd, 1H, CH_2–C≡C, ^2J=16.5 Hz, ^3J=4.4 Hz), 4.52 (d, 1H, Ph–CH_2, ^2J=15.4 Hz), 5.04 (d, 1H, C6–H, ^3J=12.1 Hz), 5.39 (d, 1H, Ph–CH_2, ^2J=15.4 Hz), 6.94 (d, 2H, arom., ^3J=7.0 Hz), 7.13 (m, 3H, arom.), 7.25–7.51 (m, 15H, arom) ppm. ^{13}C NMR: δ=18.4 (CH_2–C≡C), 45.8 (C5–H), 47.4 (Ph–CH_2), 61.5 (C6–H), 83.1, 86.6 (C≡C), 127.6, 127.7, 127.9, 128.1, 128.4, 128.5, 128.7, 128.9, 130.3 132.0 (CH arom., two signals obscured), 123.8, 134.9, 137.4, 141.0 (C quat. arom.), 156.5 (CH=N), 171.0 (C=O) ppm. ESI-MS *m*/*z* (%): 455 [M^++1] (35). $C_{32}H_{26}N_2O$ (454.56): calcd C 84.55, H 5.77, N 6.16; found: C 84.68, H 5.79, N 6.19.

4.7.8. (cis)-3-Benzyl-2,6-diphenyl-5-(3-phenyl-prop-2-ynyl)-5,6-dihydro-3H-pyrimidin-4-one ***5′c****(cis)*

Eluent for chromatography: PE/TEA (9:1).Yellow solid. Pf 105–107 °C. IR (KBr) ν=1701 (C=O), 1638 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.38 (dd, 1H, CH_2–C≡C, ^2J=17.6 Hz, ^3J=8.8 Hz), 2.96 (dd, 1H, CH_2–C≡C, ^2J=17.6 Hz, ^3J=6.2 Hz), 3.33 (dt, 1H, C5–H, ^3J=6.2, 8.8 Hz), 4.87 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 5.01 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 5.35 (d, 1H, C6–H, ^3J=6.2 Hz), 6.98 (m, 2H, arom.), 7.30–7.54 (m, 18H, arom) ppm. ^{13}C NMR: δ=16.5 (CH_2–C≡C), 44.9 (C5–H), 47.7 (Ph–CH_2), 60.3 (C6–H), 83.2, 86.9 (C≡C), 127.9, 128.1, 128.5, 128.6, 128.7, 128.8, 130.4, 131.9 (CH arom., four signals obscured), 123.7, 135.1, 136.5, 136.8 (C quat. arom.), 157.1 (CH=N), 171.2 (C=O) ppm. EIMS *m*/*z* (%): 454 [M^+] (33). $C_{32}H_{26}N_2O$ (454.56): calcd. C 84.55, H 5.77, N 6.16; found: C 84.50, H 5.74, N 6.18.

4.7.9. (trans)-3-Benzyl-5-[3-(4-chlorophenyl)-prop-2-ynyl]-2,6-diphenyl-5,6-dihydro-3H-pyrimidin-4-one ***5d****(trans)*

Eluent for chromatography: PE/TEA (8:2).Yellow oil. IR (KBr) ν=1698 (C=O), 1638 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.32 (dd, 1H, CH_2–C≡C, ^2J=16.6 Hz, ^3J=4.4 Hz), 2.88 (dt, 1H, C5–H, ^3J=4.4, 12.3 Hz), 3.10 (dd, 1H, CH_2–C≡C, ^2J=16.6 Hz, ^3J=4.4 Hz), 4.49 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 4.93 (d, 1H, C6–H, ^3J=12.3 Hz), 5.33 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 6.90 (d, 2H, arom., ^3J=6.6 Hz), 7.13 (m, 3H, arom.), 7.26–7.44 (m, 14H, arom) ppm. ^{13}C NMR: δ=18.3 (CH_2–C≡C), 45.7 (C5–H), 47.5 (Ph–CH_2), 61.5 (C6–H), 81.8, 87.7 (C≡C), 127.6, 127.7, 127.9, 128.0, 128.5, 128.7, 128.9, 130.3, 133.2 (CH arom., two signals obscured), 122.2, 134.0, 134.8, 137.4, 140.9 (C quat. arom.), 156.5 (CH=N), 170.9 (C=O) ppm. ESI-MS *m*/*z* (%): 489 [M^++1] (100). $C_{32}H_{25}ClN_2O$ (489.01): calcd C 78.60, H 5.15, N 5.73; found: C 78.48, H 5.17, N 5.70.

4.7.10. (cis)-3-Benzyl-5-[3-(4-chlorophenyl)-prop-2-ynyl]-2,6-diphenyl-5,6-dihydro-3H-pyrimidin-4-one ***5′d****(cis)*

Eluent for chromatography: PE/TEA (8:2).Yellow oil. IR (KBr) ν=1699 (C=O), 1639 (C=C/C=N) cm^{-1}. ^1H NMR: δ=2.32 (dd, 1H, CH_2–C≡C, ^2J=17.4 Hz, ^3J=8.4 Hz), 2.86 (dd, 1H, CH_2–C≡C, ^2J=17.4 Hz, ^3J=6.0 Hz), 3.28 (dt, 1H, C5–H, ^3J=6.0, 8.4 Hz), 4.86 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 4.96 (d, 1H, Ph–CH_2, ^2J=15.0 Hz), 5.28 (d, 1H, C6–H, ^3J=6.0 Hz), 6.96 (m, 2H, arom.), 7.21–7.47 (m, 17H, arom) ppm. ^{13}C NMR: δ=16.4 (CH_2–C≡C), 44.9 (C5–H), 47.6 (Ph–CH_2), 60.3 (C6–H), 82.0, 88.0 (C≡C), 127.8, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 130.4, 133.1 (CH arom.), 122.2, 134.1, 135.0, 136.6, 136.8 (C quat. arom.), 157.1 (CH=N), 171.1 (C=O) ppm. ESI-MS *m*/*z* (%): 489 [M^++1] (100). $C_{32}H_{25}ClN_2O$ (489.01): calcd C 78.60, H 5.15, N 5.73; found: C 78.69, H 5.12, N 5.73.

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