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Divergent and solvent dependent reactions of 4-ethoxycarbonyl-3-methyl-1-*tert*-butoxycarbonyl-1,2-diaza-1,3-diene with enamines

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Abstract—Starting from 1-*tert*-butyloxycarbonyl-3-methyl-4-ethoxycarbonyl-1,2-diaza-1,3-diene and β,β,β and α,β-substituted enamines a careful choice of solvents and temperatures allows the divergent synthesis of 5,6-dihydro-4*H*-pyridazines, 2-(1-*N*-boc-hydrazono-ethyl)-4-pyrrolidin-1-yl-but-3-enoic acid ethyl ester, and 1-amino-pyrroles. Moreover, some interesting conclusions about the mechanism(s) of the reaction have been drawn by careful analysis of products' structure and distribution. Thus, the reaction may proceed through a stereospecific [4+2] cycloaddition mechanism giving rise to 5,6-dihydro-4*H*-pyridazines or by simple addition or domino addition/cyclization pathways affording, respectively, 2-(1-*N*-boc-hydrazono-ethyl)-4-pyrrolidin-1-yl-but-3-enoic acid ethyl ester and 1-amino-pyrroles (formally the [3+2] cycloaddition product).

1. Introduction

The chemical properties of 1,2-diaza-1,3-diene systems mainly deal with the easy regioselective nucleophilic attack at the terminal carbon atom of the heterodiene system by a wide range of carbon and hetero-nucleophiles. This attack produces, through a Michael-type addition, α-functionalized hydrazones which frequently are not isolable and evolve, inter alias, toward the formation of heterocyclic rings by annulation reactions involving one of the diene nitrogen atoms and the appropriate functionalities located on the attacking nucleophile or on the starting 1,2-diaza-1,3-diene. Moreover, these reactions do not require anhydrous solvents or inert atmosphere and generally can be carried out under mild conditions, in one-pot fashion and entail only simple work-up procedures. Thus, during the last 30 years, using this synthetic approach, a great number of pyrroles, pyrazoles, imidazoles, thiazoles, selenazoles, 1,2,3-thiadiazoles, 1,2,3-selenadiazoles, pyridazines, pyrazines, 1,2,4-triazines and mixed heterocyclic systems have been obtained.[1]

Moreover, 1,2-diaza-1,3-dienes are able to participate in inverse electron-demand Diels–Alder reactions with electron-rich dienophiles giving rise mainly to 1,4,5,6-tetrahydropyridazines and the presence on the diene terminal carbon atom of an electron-withdrawing group allows to attain a high degree of chemo and regiocontrol.[2] Therefore, conjugated 4-chloro- or 4,4-dichloro-1,2-diaza-1,3-dienes, generated in situ from the corresponding hydrazones with Hünig's base, participate in inverse electron-demand Diels–Alder reactions with electron-rich vinyl ethers and enamines giving rise mainly to 1,2,5,6-tetrahydropyridazines.[3] The reported reactions were performed in dichloromethane, carbon tetrachloride or tetrahydrofuran and generally occur with good regio- and chemoselectivity even if seldom some drawback related to scarce selectivity was encountered.

Earlier works reported by Sommer account for [3+2] and [4+2] cycloaddition reactions of several 4-alkoxycarbonyl-1,2-diaza-1,3-dienes with cyclopentanone-derived enamines and 9-vinylcarbazole giving rise, in low to moderate yields, to octahydro-cyclopenta[*b*]indole and 9-pyridazin-3-yl-9*H*-carbazole.[4]

Recently, 4-alkoxycarbonyl-1,2-diaza-1,3-dienes were used as substrates in Diels–Alder reactions with vinyl (thio)ethers in water. Also in this case [4+2] adducts are the main

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reaction products and 1,2,5,6-tetrahydropyridazines were isolated in moderate to good yields, with high degree of stereochemical and regiochemical control, accompanied, in some cases, by pyrroles formally arising from zwitterionic [3+2] cycloaddition.[5] Finally, in a paper of recent publication, a simple one-pot protocol for the synthesis of highly functionalized 1-aminopyrrolines and oxazoline-fused 1-aminopyrrolines has been reported starting from 1,2-diaza-1,3-dienes and 3-dimethylaminopropenoates.[1j] The reactions proceed through a formal [3+2] cycloaddition reaction involving a zwitterionic intermediate generated by nucleophilic attack of the enaminic C-2 carbon atom of 3-dimethylaminopropenoates at the terminal carbon of the azo–ene system followed by a single or double cyclization step.

Starting from these results, we envisaged the opportunity to explore the behavior of 4-alkoxycarbonyl-1,2-diaza-1,3-dienes with enamines β, ββ and αβ-substituted with simple alkyl and/or aryl groups and report here the full details of our investigations. Owing to the instability of the enamine function in water all reactions were performed in dry solvents.

In particular, we describe the solvent dependent, divergent synthesis of various functionalized pyrroles and pyridazines starting from 1-*tert*-butyloxycarbonyl-3-methyl-4-ethoxycarbonyl-1,2-diaza-1,3-diene **1** and β, ββ and αβ-substituted enamines **2a**–**n**.

2. Results

1,2-Diaza-1,3-diene[1a] **1** and enamines[6] **2** were synthesized by well known procedures and were isolated as 93:7 *E*/*Z*[5] and *E* isomers, respectively.

1,2-Diaza-1,3-diene **1** was initially reacted with β-monosubstituted pyrrolidinoenamines **2a** and **2b** in methanol at 0 °C and, under these conditions, the corresponding hydrazones **3a**,**b** and 5,6-dihydro-4*H*-pyridazines **4a**,**b** were isolated after chromatographic purification over silica gel (Scheme 1).

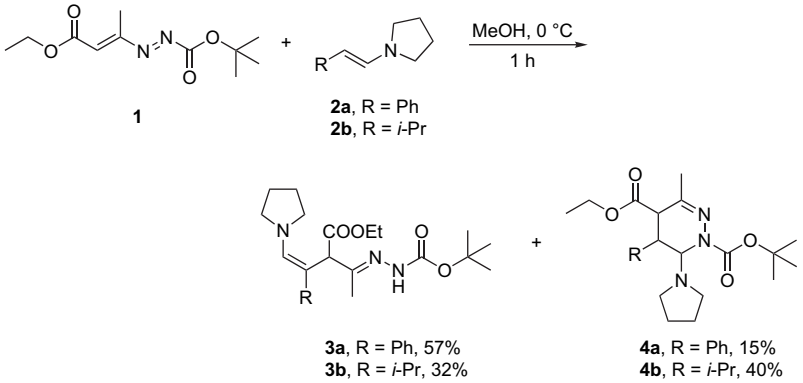
The structures of compounds **3** and **4** were assigned on the basis of analytical and spectral data. In particular, for hydrazone **3** the occurrence of only one D_2O-exchangeable hydrogen atom and one C_{sp^3}–H in the ^1H NMR spectrum allowed us to rule out the existence of tautomeric hydrazine and 1-aza-1,3-butadiene derivatives, whereas NOESY experiment allows to attribute the geometry around the carbon–carbon double bond (Fig. 1). Moreover, 5,6-dihydro-4*H*-pyridazines **4a**,**b** were recognized by mono and bidimensional nuclear magnetic resonance analyses as reported in Figure 1 for **4b**. In first instance, the stereochemistry of **4b** was tentatively assigned comparing NMR spectroscopic data with dihedral angle and interatomic distances calculated at molecular mechanics level for all conceivable isomers.

The structures of the four possible diastereoisomers of **4b** (4,5-(*Z*)/5,6-(*Z*), 4,5-(*Z*)/5,6-(*E*), 4,5-(*E*)/5,6-(*Z*), 4,5-(*E*)/5,6-(*E*)) were subjected to an extensive conformational analysis using the MM+ force field.[7] The ring framework of each isomer could theoretically exist in two different conformations in which substituents on C-4, C-5, and C-6 could exist in a *pseudo*-axial or *pseudo*-equatorial position. The conformational search showed that the energy differences between the couples of conformational isomers are about 3–6 kcal/mol. Only the favorite conformer of the 4,5-(*E*)/5,6-(*E*) isomer in which the substituents at C-4, C-5, and C-6 are in a *pseudo*-axial position, showed the geometrical parameters in agreement with measured H–H coupling constants and observed NOE interactions (Fig. 1). Moreover, the matching structure is also the energetically favored among the possible isomers. It is worth noting that a subsequent X-ray diffraction analysis on crystals of compound **4b** perfectly confirmed the calculated structure as depicted in the ORTEP-III plot (Fig. 2).[8] This result validated the theoretical/analytical MM/NMR approach as reliable tool for the determination of stereochemical relationship.

Moreover, when pure hydrazones **3a**,**b** were heated under reflux in methanol, the corresponding 1-amino-pyrroles **5a**,**b** were isolated in almost quantitative yields by usual work-up procedures, thus ruling out the intermediacy of hydrazones **3** in 5,6-dihydro-4*H*-pyridazines **4** formation (Scheme 2).

Finally, when pure 5,6-dihydro-4*H*-pyridazines **4a**,**b** were treated with Amberlyst 15 in ethanol at room temperature, the corresponding 3-methyl-1,4-dihydro-pyridazine-4-carboxylic acid ethyl esters **6a**,**b** were isolated in almost quantitative yields (Scheme 3).

Hence, encouraged by these results, we investigated the possibility of extending the reactions of **1** with enamines



Scheme 1.

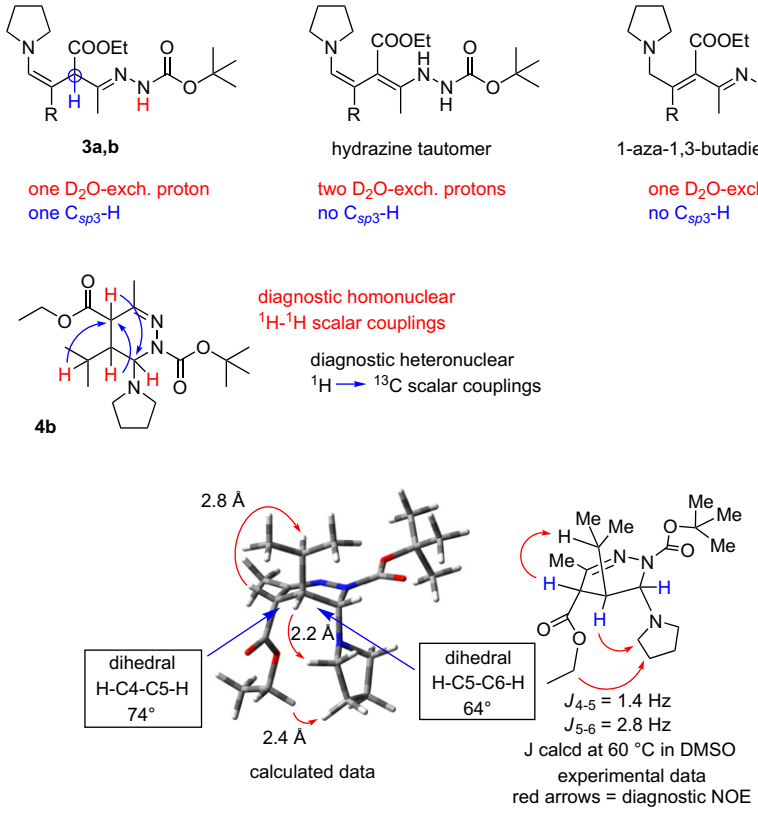
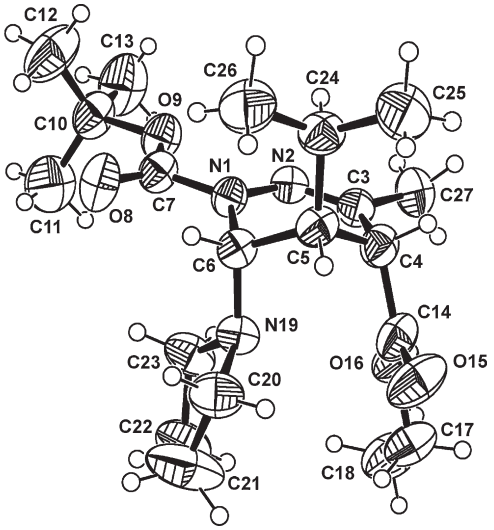


Figure 1.

2a,**b** to the chemoselective formation of the hydrazone/pyrrole **3/5** or pyridazine **4** through the appropriate choice of solvents and reaction temperatures. A comprehensive review of tested conditions and obtained results are summarized in Table 1.

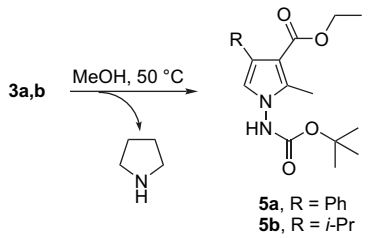
All reactions were performed in 0.25 mM solutions using dry solvents with increasing polarity. The E_T^N scale has been chosen as a measure of solvents' polarity because this empirical parameter gave satisfactory quantitative description of medium effects just intended as the overall solvation power depending on the contribution of all possible, non specific and specific, intermolecular interactions between solute ions or molecules and solvent molecules.[9]

As reported in Table 1, entries 1–4, the reactions performed with less polar solvents such as cyclohexane, *n*-hexane, toluene, or tetrahydrofuran gave almost exclusively the 5,6-dihydro-4*H*-pyridazines **4a**,**b** and the best results have been obtained while working in *n*-hexane at −78 °C. Whereas,

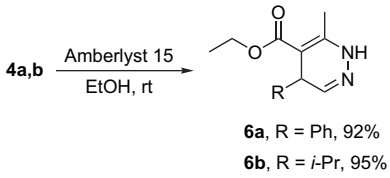


ORTEPIII plot of compound **4a** in the asymmetric unit showing the numbering schemes for all non-hydrogen atoms. Ellipsoids drawn at 50% probability.

Figure 2.



Scheme 2.



Scheme 3.

increasing the solvent polarity yielded the mixtures of hydrazones **3a**,**b** and pyridazines **4a**,**b** as reported in Table 1, entries 5 and 6, for the reactions performed in chloroform or acetonitrile at 0 °C. Better results can be obtained lowering the reaction temperature or using a polar and protic solvent such as methanol at −78 °C, entries 7–9. Under these conditions hydrazones **3a**,**b** can be isolated in good yields. Finally, using methanol as solvent and performing the reactions at −78 °C, the TLC analysis of the reaction mixtures shown after few minutes the complete disappearance of the azoalkene **1** and the formation of hydrazones **3a**,**b** as the sole products. Thus, warming the reaction to room temperature and then heating to 50 °C for 1 h resulted in the isolation of pyrroles **5a**,**b** in 76 and 68% yields, respectively (Scheme 4; Table 1, entry 10).

Therefore, in order to check the synthetic efficiency of the procedures appointed for the chemoselective synthesis of 5,6-dihydro-4*H*-pyridazines **4** (entry 2), hydrazones **3** (entry 9), and pyrroles **5** (entry 10), we tested the reactivity of azoalkene **1** with a new group of enamines (Scheme 5, Table 2).

As reported in Scheme 5 and Table 2, β-substituted enamines **2c–e** showed the same behavior as structurally related compounds **2a**,**b** giving rise to the corresponding pyridazines **4c–e**, hydrazones **3c**,**d**, and pyrroles **5c**,**d** in good yields. The sole exception is represented by the reaction of **1** with the encumbered enamine **2e** in methanol, which do not react at all at −78 °C, giving rise to a mixture of **4e** and **7**[8] after prolonged stirring at 0 °C.

Moreover, αβ and ββ-disubstituted enamines, **2g–i** and **2j**,**k**, show the same behavior both in apolar or polar solvents, at temperatures ranging from −78 °C to room temperature, giving rise, respectively, to fused 1-aminopyrroles **5e–h** or 1-amino-5-hydroxypyrroles **5i–j** in very good yields, whereas enamine **2f** yielded under the same conditions the of hydrazone **3e**, which in turn could be thermally converted into the corresponding pyrrole **5e**.

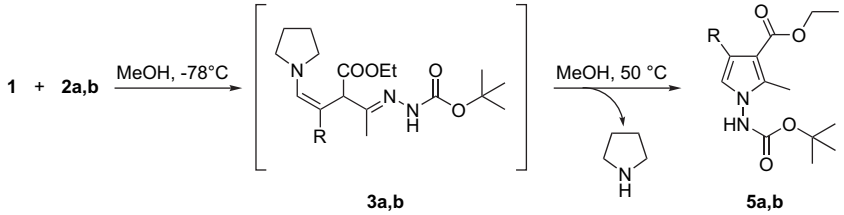
3. Discussion

On the basis of the obtained results, it would be reasonable to postulate that the reactions between 1,2-diaza-1,3-diene **1** and enamines **2a–e** proceed in hexane and methanol through two different mechanisms giving rise to 5,6-dihydro-4*H*-pyridazines **4a–e** and hydrazones **3a–d**, respectively. Thus, working in hexane, the azoalkene **1** acts as heterodiene in an inverse electron-demand Diels–Alder reaction with the electron-rich dienophiles **2**. The reactions occur in a regio- and stereocontrolled fashion, the *endo*-adducts **4a–e** are the sole isolated compounds and the stereochemistry of both diene and dienophile is retained in the final compounds.

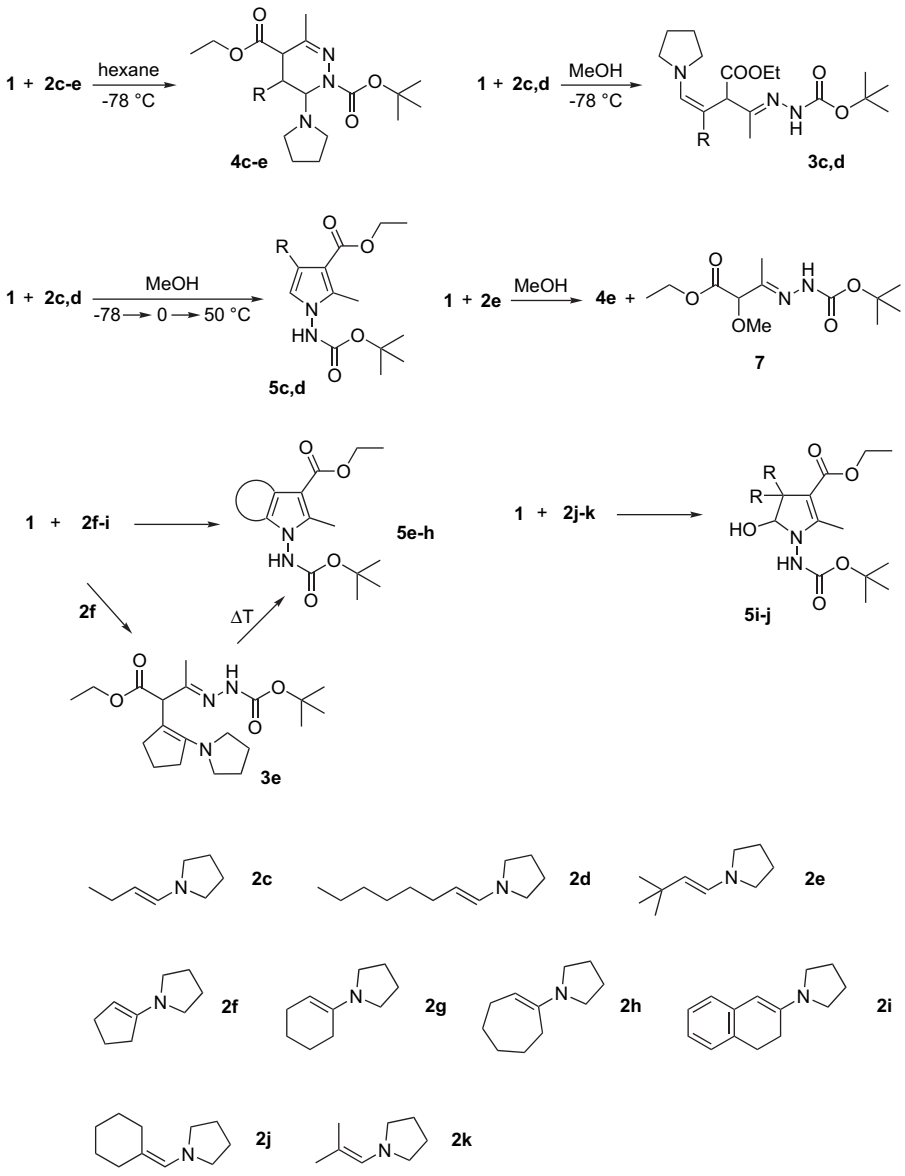
As mentioned above, the diene **1** exists as a 93:7 mixture of *E* and *Z* isomers, however, the presence of the *Z* isomer did not

Table 1. Tested solvents for the reaction of **1** with **2a**,**b**

Entry	Solvent	E_T^N	*T* (°C)	Time (min)	**3a** (%)	**4a** (%)	**5a** (%)	**3b** (%)	**4b** (%)	**5b** (%)
1	Cyclohexane	0.006	0	30	—	79	—	3	73	—
2	*n-Hexane*	*0.009*	*−78*	*60*	—	*82*	—	—	*85*	—
3	Toluene	0.099	0	30	9	57	—	2	72	—
4	Tetrahydrofuran	0.207	0	30	—	74	—	—	75	—
5	Chloroform	0.259	0	30	35	39	—	41	27	—
6	Acetonitrile	0.460	0	10	18	56	—	21	45	—
7	Acetonitrile	0.460	−40	60	65	21	—	48	16	—
8	Methanol	0.764	0	10	52	18	—	31	30	—
9	*Methanol*	*0.764*	*−78*	*120*	*72*	—	—	*65*	*5*	—
10	*Methanol*	*0.764*	*−78→50*	*120/60*	—	—	*76*	—	*3*	*68*



Scheme 4.



Scheme 5.

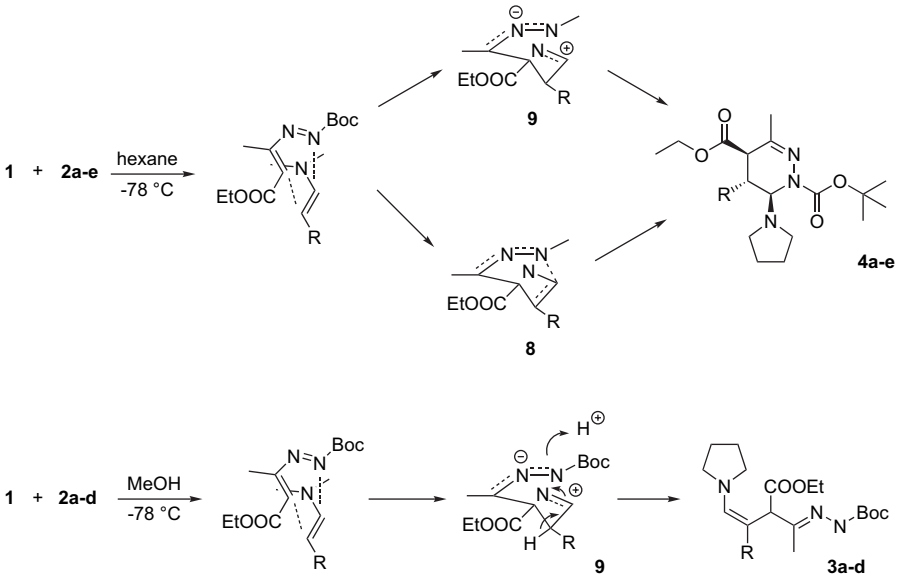
influence to any extent the reaction outcome, and any compound arising from the cycloaddition reaction of the *Z* isomer was detectable by ^{1}H NMR analysis of the reaction mixture.

However, in our opinion, a concerted synchronous reaction mechanism is unlikely mainly since both the reactants are highly polarized and their chemistry is characterized by

Table 2. Reactions of **1** with **2c–k**

Enamine	Solvent	Temperature (°C)	Time	**3**	**4**	**5**
2c	Hexane	−78	60’	—	83	—
2c	Methanol	−78	24 h	68	—	—
2c	Methanol	−78→50	24 h/60’	—	—	76
2d	Hexane	−78	60’	—	68	—
2d	Methanol	−78→0	4/12 h	52	—	—
2d	Methanol	−78→0→50	4 h/12 h/60’	—	—	63
2e	Hexane	−78	24 h	—	75	—
2e[a]	Methanol	−78→0	4/12 h	—	16	—
2f	Hexane or methanol	−78 or 0 or rt	30’	80–86	—	—
2g	Hexane or methanol	−78 or 0 or rt	30’	—	—	85–89
2h	Hexane or methanol	−78 or 0 or rt	30’	—	—	76–82
2i	Hexane or methanol	−78 or 0 or rt	30’	—	—	82–90
2j	Hexane or methanol	−78 or 0 or rt	30’	—	—	65–78
2k	Hexane or methanol	−78 or 0 or rt	30’	—	—	73–85

[a] Beside **4e** compound **7** was isolated in 17% yield (Scheme 4).

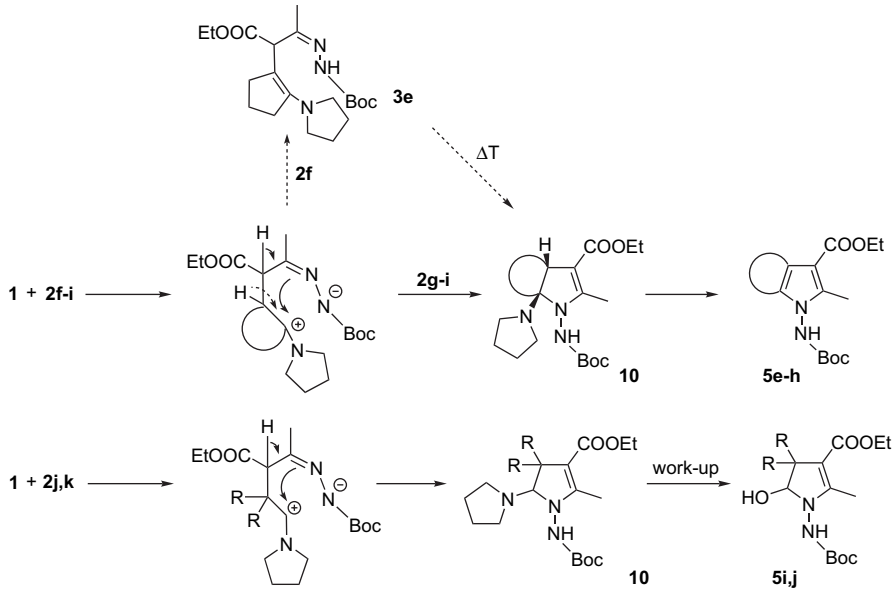


Scheme 6.

pronounced charge alternation. Thus, an alternative asynchronous or polar stepwise mechanism may be proposed involving, respectively, the formation of one σ-bond in advance with respect to the other one (**8**) or the nucleophilic attack of β-carbon atom of the enamine on the electrophilic terminus of diene system giving rise to a zwitterionic intermediate **9**. Both these intermediates could evolve toward the formation of 5,6-dihydro-4*H*-pyridazines **4a**–**e** in the final step (Scheme 6). Nevertheless, working in hexane, the intermediacy of non-charged specie like **8** is more liable.

At a first glance, the suggested mechanisms might appear inadequate to explain the stereospecificity of a Diels–Alder reaction, however, if the proposed intermediates can change into the products before any internal rotation occurs, also an asynchronous or polar stepwise mechanism can account for the observed stereospecificity.[2f] Another feature supporting a non-concerted reaction pathway is the high solvent effect on the reaction outcome.[2f] Thus, when the reactions were performed in methanol (polar and protic solvent) at −78 °C, hydrazones **3a**,**b**, arising from zwitterionic intermediate **9** through a fast solvent mediated proton exchange, are the sole reaction products (Table 1, entry 9). Whereas working in acetonitrile (polar and aprotic solvents), **3a**,**b** became the main products at −40 °C (Table 1, entry 7) while lowering the reaction temperature at −78 °C the reaction did not get going at all.

On the contrary, the reactions of 1,2-diaza-1,3-diene **1** with αβ and ββ-disubstituted enamines, **2f**–**i** and **2j**,**k**, are independent of solvent polarity and probably entails a stepwise addition of the enamine to the azoalkene followed by cyclization of the N-2 anion on the electrophilic carbon atom to give dihydropyrroles **10** (Scheme 7). The cyclization step



Scheme 7.

is always faster than proton exchange with the exception of the reaction performed between **1** and enamine **2f** giving rise to the open chain adduct **3e** and this behavior is probably correlated to steric strain in the cyclization step. Furthermore, primary cyclization adducts **10**, obtained from **1** and enamines **2g–i**, evolve spontaneously to the corresponding pyrroles **5f–h** by loss of pyrrolidine, whereas 4,4-disubstituted intermediate from enamines **2j**,**k** was isolated as the corresponding 5-hydroxy derivatives **5i**,**j**, the hydrolytic process taking place during the aqueous work-up of the crude reaction mixture.

The last sentence has been established by ^{1}H NMR analysis of crude **5i**,**j** obtained by simple evaporation of the solvent showing the presence of both amino and hydroxy derivatives. Furthermore, the signal pattern of the sole hydroxy derivatives **5** can be detected by ^{1}H NMR after the addition of several drops of water to the NMR test-tube.

In summary, some new and fundamentals aspects of the reactivity of the 1,2-diaza-1,3-dienes with electron-rich enamines has been described. In particular, we reported the chemoselective formation of a variety of pyridazines and pyrroles in good to excellent yields starting from the same reactants by straightforward variation of reaction medium and temperatures. From the synthetic point of view and with respect to previously reported results, these methodologies override most of the drawback related to the effectiveness of competitive reaction mechanisms.[3,4]

In addition to the synthetic efficiency, some interesting remarks on the reaction mechanism(s) have been made by careful analysis of products' structure and distribution even if no attempts were made to establish the mechanistic details of all reported reactions.

4. Experimental

4.1. General

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F_{254} thin-layer plates were employed for thin layer chromatography (TLC). Silica gel 40–63 μm/60 Å was employed for flash column chromatography. Melting points are uncorrected. Infrared spectra were recorded on a FTIR spectrophotometer using KBr tablets for solids and NaCl disks for oils. Unless otherwise stated, proton NMR spectra were recorded at room temperature in $CDCl_3$, at 200 MHz, with residual chloroform as the internal reference (δ_H= 7.27 ppm). ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ 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 (COSY, HETCOR, NOESY) were used, where appropriate, to aid in the assignment of signals in the proton spectra. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ ADVANTAGE AP-electrospray/ion trap equipped instrument using a syringe pump device for the direct injection of sample solutions. 'PE' refers to the fraction of petroleum ether with boiling point of 40–60 °C. 'EtOAc' means ethyl acetate and 'TEA' means triethylamine. 1,2-1,2-Diaza-1,3-diene[1a] **1** and enamines[6] **2** were synthesized by well known procedures and were isolated as 93:7 *E*/*Z*[5] and *E* isomers, respectively. Compound **7** was identified by comparison (^{1}H NMR, MS) with an authentic sample.[10]

4.2. *tert*-Butoxycarbonyl-hydrazones 3a–e

4.2.1. (E)-2-[1-(*tert*-Butoxycarbonyl-hydrazono)-ethyl]-3-phenyl-4-pyrrolidin-1-yl-but-3-enoic acid ethyl ester 3a. A solution of the 1,2-diaza-1,3-butadiene **1** (1 mmol, 0.242 g) in dry methanol (4 ml) was slowly dropwise added to a well stirred solution of the enamine **2a** (1.1 mmol, 0.190 g) in methanol (4 ml), and cooled at −78 °C. The obtained mixture was stirred at −78 °C for 2 h then poured in water (50 ml) and extracted twice with ethyl acetate (2×25 ml). The organic layer was dried over Na_2SO_4, evaporated to dryness, and the crude product purified by flash chromatography eluting with PE/EtOAc, 8:2. White solid; mp 60–63 °C; R_f (30% EtOAc/PE) 0.48; IR (cm^{-1}): 3287, 1727, 1687, 1621; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, CH_3, ^3J=7 Hz), 1.47 (s, 9H, $(CH_3)_3$), 1.79–1.82 (m, 4H, CH_2), 2.27 (s, 3H, CH_3), 2.58–2.74 (m, 4H, CH_2N), 3.84–4.08 (m, 3H, CH_2O, CH), 4.60 (d, 1H, =CH, ^4J=2.0 Hz), 6.56 (br s, 1H, NH, D_2O-exch.), 7.12–7l.36 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$) δ 10.9, 13.5, 23.0, 27.5, 45.5, 45.9, 58.0, 81.5, 87.1, 101.5, 126.1, 128.0, 128.2, 145.1, 155.2, 159.2, 166.3. ESIMS *m*/*z* (%): 416 [M$^+$+1] (100); ESIMS/MS *m*/*z* (%): 344 (75), 288 (100); $C_{23}H_{33}N_3O_4$ (415.53): calcd. C, 66.48; H, 8.00; N, 10.11. Found: C, 66.42; H, 7.94; N, 10.06.

4.2.2. 2-[1-(*tert*-Butoxycarbonyl-hydrazono)-ethyl]-4-methyl-3-[1-pyrrolidin-1-yl-meth-(*Z*)-ylidene]-pentanoic acid ethyl ester 3b. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (30% EtOAc/PE) 0.43; IR (cm^{-1}): 3275, 1746, 1698; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, 3H, CH_3, ^3J=7.0 Hz), 0.93 (d, 3H, CH_3, ^3J=7.0 Hz), 1.26 (t, 3H, CH_3, ^3J=7.0 Hz), 1.47 (s, 9H, $(CH_3)_3$), 1.68–1.77 (m, 4H, CH_2), 2.18 (s, 3H, CH_3), 2.42–2.60 (m, 5H, CH_2N, CH), 2.73 (s, 1H, CH), 4.04–4.23 (m, 2H, CH_2O), 4.37 (s, 1H, =CH), 6.44 (br s, 1H, NH, D_2O-exch.); ^{13}C NMR ($CDCl_3$) δ 10.9, 11.5, 14.6, 23.8, 23.9, 25.7, 28.4, 46.6, 59.3, 81.6, 117.2, 137.6, 155.7, 159.3, 167.1. ESIMS *m*/*z* (%): 382 [M$^+$+1] (100); ESIMS/MS *m*/*z* (%): 310 (100), 254 (80); $C_{20}H_{35}N_3O_4$ (381.51): calcd. C, 62.96; H, 9.25; N, 11.01. Found: C, 62.68; H, 9.21; N, 10.95.

4.2.3. 2-[1-(*tert*-Butoxycarbonyl-hydrazono)-ethyl]-3-[1-pyrrolidin-1-yl-meth-(*Z*)-ylidene]-pentanoic acid ethyl ester 3c. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (30% EtOAc/PE) 0.52; IR (cm^{-1}): 3274, 1728, 1682, 1613; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3, ^3J=7.3 Hz), 1.15–1.37 (m, 5H, CH_3, CH_2), 1.47 (s, 9H, $(CH_3)_3$), 1.70–1.80 (m, 4H, CH_2), 2.16 (s, 3H, CH_3), 2.55–2.68 (m, 4H, CH_2N), 2.68–2.78 (m, 1H, CH), 4.02–4.22 (m, 2H, CH_2O), 4.28 (s, 1H, =CH), 6.52 (br s, 1H, NH, D_2O-exch.); ^{13}C NMR ($CDCl_3$) δ 10.8, 11.7, 14.6, 20.2, 23.8, 28.4, 28.7, 47.0, 59.3, 82.4, 118.4, 137.9, 154.5, 158.9, 165.9. ESIMS *m*/*z* (%): 369 [M$^+$+1] (100); ESIMS/MS *m*/*z* (%): 296 (100), 240 (20); $C_{19}H_{33}N_3O_4$ (367.48): calcd. C, 62.10; H, 9.05; N, 11.43. Found: C, 62.08; H, 9.12; N, 11.51.

4.2.4. 2-[1-(*tert*-Butoxycarbonyl-hydrazono)-ethyl]-3-[1-pyrrolidin-1-yl-meth-(*Z*)-ylidene]-nonanoic acid ethyl ester 3d. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (20% EtOAc/PE) 0.36; IR (cm^{-1}): 3291, 1729, 1681, 1613; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3, ^3J=7.0 Hz), 1.15–1.38 (m, 13H, CH_3, CH_2), 1.40–1.53 (m, 12H, $(CH_3)_3$, CH_2), 1.70–1.80 (m, 4H, CH_2), 2.15 (s, 3H, CH_3), 2.52–2.68 (m, 4H, CH_2N), 2.70–2.77 (m, 1H, CH), 4.02–4.22 (m, 2H, CH_2O), 4.27 (s, 1H, =CH), 6.65 (br s, 1H, NH, D_2O-exch.); ^{13}C NMR ($CDCl_3$) δ 11.7, 14.3, 14.7, 22.8, 23.8, 26.4, 28.3, 28.5, 29.5, 32.0, 33.5, 47.0, 58.9, 81.6, 118.9, 137.6, 155.5, 158.7, 166.9. ESIMS *m/z* (%): 446 [M^++23] (55), 424 [M^++1] (100), 383 (35), 375 (40), 325 (80); ESIMS/MS *m/z* (%) (parent ion: 424): 352 (100), 324 (55), 296 (60); $C_{23}H_{41}N_3O_4$ (423.59): calcd. C, 65.22; H, 9.76; N, 9.92. Found: C, 65.13; H, 9.83; N, 10.07.

4.2.5. 3-(*tert*-Butoxycarbonyl-hydrazono)-2-(2-pyrrolidin-1-yl-cyclopent-1-enyl)-butyric acid ethyl ester 3e. Purified by flash chromatography (PE/EtOAc, 9:1); white solid; mp 124–126 °C; R_f (30% EtOAc/PE) 0.35; IR (cm^{-1}): 3285, 1737, 1650, 1589; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3, ^3J=7.3 Hz), 1.47 (s, 9H, $(CH_3)_3$), 1.60–2.00 (m, 10H, CH_2), 2.17 (s, 3H, CH_3), 2.43–260 (m, 2H, CH_2N), 2.62–2.75 (m, 2H, CH_2N), 3.13–3.16 (m, 1H, CH), 4.04–4.22 (m, 2H, CH_2O), 6.18 (br s, 1H, NH, D_2O-exch.); ^{13}C NMR ($CDCl_3$) δ 11.7, 15.0, 24.4, 24.6, 28.5, 35.1, 35.9, 44.5, 47.3, 59.1, 81.6, 95.6, 99.4, 156.1, 159.4, 167.3. ESIMS *m/z* (%): 380 [M^++1] (100), 309 (25); ESIMS/MS *m/z* (%): 308 (100); $C_{20}H_{33}N_3O_4$ (379.49): calcd. C, 63.30; H, 8.76; N, 11.07. Found: C, 63.28; H, 8.81; N, 11.12.

4.3. 5,6-Dihydro-4*H*-pyridazines 4a–e

4.3.1. 3-Methyl-5-phenyl-6-pyrrolidin-1-yl-5,6-dihydro-4*H*-pyridazine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester 4a. A solution of the 1,2-diaza-1,3-butadiene **1** (1 mmol, 0.242 g) in dry hexane (4 ml) was slowly dropwise added to a well stirred solution of the enamine **2a** (1.1 mmol, 0.190 g) in hexane (4 ml), and cooled at −78 °C. The obtained mixture was stirred at −78 °C for 1 h then poured in water (50 ml) and extracted twice with ethyl acetate (2×25 ml). The organic layer was dried over Na_2SO_4, evaporated to dryness, and the crude product purified by flash chromatography eluting with PE/EtOAc, 9:1. White solid mp 119–121 °C; R_f (10% EtOAc/PE) 0.42; IR (cm^{-1}): 1722, 1650; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, CH_3, ^3J=7.0 Hz), 1.40 (s, 9H, $(CH_3)_3$), 1.60–1.70 (m, 4H, CH_2), 2.29 (s, 3H, CH_3), 2.40–2.52 (m, 2H, CH_2N), 2.66–2.80 (m, 2H, CH_2N), 2.97 (s, 1H, CH-4), 3.93 (d, 1H, CH-5, ^3J=2.2 Hz), 3.95–4.09 (m, 1H, CH_2O), 4.10–4.24 (m, 1H, CH_2O), 4.76 (d, 1H, CH-6, ^3J=2.2 Hz), 7.04–7.11 (m, 2H, arom.), 7.14–7.32 (m, 3H, arom:); ^{13}C NMR ($CDCl_3$) δ 10.8, 14.2, 23.9, 28.4, 40.7, 45.1, 49.7, 61.3, 81.8, 127.4, 127.5, 128.9, 139.5, 146.9, 153.1, 169.8. ESIMS *m/z* (%): 416 [M^++1] (95), 289 (40), 243 (100); ESIMS/MS *m/z* (%) (parent ion: 416): 359 (30), 288 (100); $C_{23}H_{33}N_3O_4$ (415.53): calcd. C, 66.48; H, 8.00; N, 10.11. Found: C, 66.35; H, 7.87; N, 10.23.

4.3.2. 5-Isopropyl-3-methyl-6-pyrrolidin-1-yl-5,6-dihydro-4*H*-pyridazine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester 4b. Purified by flash chromatography (PE/EtOAc, 9:1); white solid; mp 72–74 °C; R_f (10% EtOAc/PE) 0.53; IR (cm^{-1}): 1723, 1698; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.93 and 0.96 (d, 3H, CH_3, ^3J=6.6 Hz), 1.14–1.30 (m, 4H, CH_3, CH), 1.52 (s, 9H, $(CH_3)_3$), 1.55–1.65 (m, 4H, CH_2), 2.16 (s, 3H, CH_3), 2.20–2.30 (m, 1H, CH-5), 2.312–2.39 (m, 2H, CH_2N), 2.56–2.66 (m, 2H, CH_2N), 2.78 (s, 1H, CH-4), 3.81–4.00 (m, 1H, CH_2O), 4.04–4.21 (m, 1H, CH_2O), 4.73 (s, 1H, CH-6). ^{13}C NMR ($CDCl_3$) δ 14.2, 20.9, 21.6, 23.7, 25.7, 27.5, 28.5, 42.3, 43.7, 49.6, 60.9, 68.3, 81.3, 146.9, 153.1, 170.3. ESIMS *m/z* (%): 382 [M^++1] (100), 255 (20); ESIMS/MS *m/z* (%) (parent ion: 382): 310 (40), 254 (100); $C_{20}H_{35}N_3O_4$ (381.51): calcd. C, 62.96; H, 9.25; N, 11.01. Found: C, 62.87; H, 9.34; N, 10.88.

4.3.3. 5-Ethyl-3-methyl-6-pyrrolidin-1-yl-5,6-dihydro-4*H*-pyridazine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester 4c. Purified by flash chromatography (PE/EtOAc, 8:2); clear oil; R_f (10% EtOAc/PE) 0.55; IR (cm^{-1}): 1723, 1698, 1634; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3, ^3J=7.1 Hz), 1.23 (t, 3H, CH_3, ^3J=7.3 Hz), 1.53 (s, 9H, $(CH_3)_3$), 1.56–1.64 (m, 4H, CH_2), 2.16 (s, 3H, CH_3), 2.30–2.42 (m, 2H, CH_2N), 2.48–2.70 (m, 4H, CH_2N, CH-4, CH-5), 3.82–4.02 (m, 1H, CH_2O), 4.04–4.22 (m, 1H, CH_2O), 4.58 (s, 1H, CH-6). ^{13}C NMR ($CDCl_3$) δ 11.8, 14.2, 23.3, 23.7, 25.6, 28.4, 36.9, 45.1, 49.6, 60.9, 68.8, 81.7, 146.2, 154.0, 170.1. ESIMS *m/z* (%): 390 [M^++23] (45), 368 [M^++1] (100), 351 (30); ESIMS/MS *m/z* (%) (parent ion: 368): 296 (50), 240 (100); $C_{19}H_{33}N_3O_4$ (367.48): calcd. C, 62.10; H, 9.05; N, 11.43. Found: C, 62.14; H, 9.12; N, 11.55.

4.3.4. 5-Hexyl-3-methyl-6-pyrrolidin-1-yl-5,6-dihydro-4*H*-pyridazine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester 4d. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (10% EtOAc/PE) 0.55; IR (cm^{-1}): 1725, 1698, 1637; ^1H NMR ($CDCl_3$) δ 0.82–0.92 (m, 6H, CH_3), 1.14–1.38 (m, 10H, CH_2), 1.52 (s, 9H, $(CH_3)_3$), 1.58–1.64 (m, 4H, CH_2), 2.15 (s, 3H, CH_3), 2.28–2.40 (m, 2H, CH_2N), 2.55–2.69 (m, 4H, CH_2N, CH-4, CH-5), 3.82–4.01 (m, 1H, CH_2O), 4.03–4.21 (m, 1H, CH_2O), 4.56 (s, 1H, CH-6). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 22.6, 23.7, 25.7, 27.4, 28.5, 29.3, 30.4, 31.8, 35.2, 45.5, 49.6, 60.9, 68.7, 81.7, 146.1, 153.4, 170.1. ESIMS *m/z* (%): 446 [M^++23] (100), 424 [M^++1] (30), 253 (25); ESIMS/MS *m/z* (%) (parent ion: 424): 367 (45), 296 (100); $C_{23}H_{41}N_3O_4$ (423.59): calcd. C, 65.22; H, 9.76; N, 9.92. Found: C, 65.41; H, 9.57; N, 11.41.

4.3.5. 5-*tert*-Butyl-3-methyl-6-pyrrolidin-1-yl-5,6-dihydro-4*H*-pyridazine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester 4e. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (10% EtOAc/PE) 0.44; IR (cm^{-1}): 1725, 1698, 1641; ^1H NMR ($CDCl_3$) δ 0.89 (s, 9H, $(CH_3)_3$), 1.23 (t, 3H, CH_3, ^3J=6.9 Hz), 1.53 (s, 9H, $(CH_3)_3$), 1.55–1.64 (m, 4H, CH_2), 2.19 (s, 3H, CH_3), 2.31–2.41 (m, 3H, CH_2N, CH-5), 2.51–2.63 (m, 2H, CH_2N), 2.69 (s, 1H, CH-4), 3.84–4.02 (m, 1H, CH_2O), 4.04–4.18 (m, 1H, CH_2O), 4.82 (br s, 1H, CH-6). ^{13}C NMR ($CDCl_3$) δ 14.2, 23.8, 25.3, 28.4, 28.5, 32.2, 41.9, 44.8, 49.5, 61.0, 66.8, 81.5, 147.8, 153.1, 170.9. ESIMS *m/z* (%): 396 [M^++1] (100); ESIMS/MS *m/z* (%): 342 (40), 324 (50), 268 (100); $C_{21}H_{37}N_3O_4$ (395.54): calcd. C, 63.77; H, 9.43; N, 10.62. Found: C, 63.68; H, 9.39; N, 10.72.

4.4. 1*H*-Pyrroles 5a–j

4.4.1. 1-*tert*-Butoxycarbonylamino-2-methyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester 5a. A solution of the 1,2-diaza-1,3-butadiene **1** (1 mmol, 0.242 g) in dry methanol (4 ml) was slowly dropwise added to a well stirred solution of the enamine **2a** (1.1 mmol, 0.190 g) in methanol (4 ml), cooled at −78 °C. The obtained mixture was stirred at −78 °C for 2 h, warmed to room temperature, and finally heated at 50 °C for 1 h. The mixture was then poured in water (50 ml) and extracted twice with ethyl acetate (2×25 ml). The organic layer was dried over Na_2SO_4, evaporated to dryness, and the crude product purified by flash chromatography eluting with PE/EtOAc, 8:2. White solid; mp 145–147 °C; R_f (20% EtOAc/PE) 0.32; IR (cm^{-1}): 3272, 1742, 1676; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, CH_3, ^3J=6.9 Hz), 1.51 (s, 9H, $(CH_3)_3$), 2.44 (s, 3H, CH_3), 4.14 (q, 2H, CH_2O, ^3J=6.9 Hz), 6.58 (s, 1H, arom), 7.10 (br s, 1H, NH, D_2O-exch.), 7.22–7.38 (m, 5H, arom). ^{13}C NMR ($CDCl_3$) δ 10.7, 14.3, 28.3, 59.7, 83.0, 109.5, 120.5, 125.0, 126.6, 127.7, 129.6, 135.4, 137.9, 154.1, 165.6. ESIMS *m/z* (%): 367 [M^++23] (100), 345 [M^++1] (30); ESIMS/MS *m/z* (%) (parent ion: 345): 298 (60), 288 (100); $C_{19}H_{24}N_2O_4$ (344.40): calcd. C, 66.26; H, 7.02; N, 8.13. Found: C, 66.15; H, 6.92; N, 8.22.

4.4.2. 1-*tert*-Butoxycarbonylamino-4-isopropyl-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester 5b. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (30% EtOAc/PE) 0.57; IR (cm^{-1}): 3277, 1746, 1699; ^1H NMR ($CDCl_3$) δ 1.17 (d, 6H, CH_3, ^3J=6.6 Hz), 1.33 (t, 3H, CH_3, ^3J=7.3 Hz), 1.48 (s, 9H, $(CH_3)_3$), 2.37 (s, 3H, CH_3), 3.34 (sextet, 1H, CH, ^3J=6.6 Hz), 4.25 (q, 2H, CH_2O, ^3J=7.3 Hz), 6.35 (s, 1H, arom), 7.15 (br s, 1H, NH, D_2O-exch.). ^{13}C NMR ($CDCl_3$) δ 10.8, 14.5, 23.7, 25.7, 28.3, 59.4, 82.5, 109.2, 117.3, 131.8, 137.7, 154.3, 165.9. ESIMS *m/z* (%): 333 [M^++23] (100), 311 [M^++1] (40); ESIMS/MS *m/z* (%) (parent ion: 311): 255 (100); $C_{16}H_{26}N_2O_4$ (310.39): calcd. C, 61.91; H, 8.44; N, 9.03. Found: C, 61.87; H, 8.35; N, 9.12.

4.4.3. 1-*tert*-Butoxycarbonylamino-4-ethyl-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester 5c. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (20% EtOAc/PE) 0.45; IR (cm^{-1}): 3272, 1747, 1698, 1678; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, CH_3, ^3J=7.7 Hz), 1.33 (t, 3H, CH_3, ^3J=7.0 Hz), 1.49 (s, 9H, $(CH_3)_3$), 2.38 (s, 3H, CH_3), 2.68 (q, 2H, CH_2, ^3J=7.7 Hz), 4.25 (q, 2H, CH_2O, ^3J=7.0 Hz), 6.35 (s, 1H, arom), 7.00 (br s, 1H, NH, D_2O-exch.). ^{13}C NMR ($CDCl_3$) δ 10.8, 14.5, 14.7, 28.3, 29.9, 59.4, 82.8, 109.7, 118.4, 126.6, 137.8, 154.2, 165.9. ESIMS *m/z* (%): 319 [M^++23] (100), 297 [M^++1] (30); ESIMS/MS *m/z* (%) (parent ion: 297): 241 (100); $C_{15}H_{24}N_2O_4$ (296.36): calcd. C, 60.79; H, 8.16; N, 9.45. Found: C, 60.57; H, 8.03; N, 9.53.

4.4.4. 1-*tert*-Butoxycarbonylamino-4-hexyl-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester 5d. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (20% EtOAc/PE) 0.54; IR (cm^{-1}): 3272, 1746, 1698; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH_3, ^3J=6.9 Hz), 1.24–1.40 (m, 9H, CH_3, CH_2), 1.42–1.54 (m, 11H, $(CH_3)_3$, CH_2), 2.38 (s, 3H, CH_3), 2.62 (t, 2H, CH_2, ^3J=6.5 Hz), 4.25 (q, 2H, CH_2O, ^3J=6.9 Hz), 6.34 (s, 1H, arom), 6.95 (br s, 1H, NH, D_2O-exch.). ^{13}C NMR ($CDCl_3$) δ 10.8, 14.3, 14.6, 22.9, 26.9, 28.3, 29.5, 30.4, 32.0, 59.4, 82.6, 109.6, 119.0, 124.8, 137.7, 154.3, 166.0. ESIMS *m/z* (%): 407 [M^++(32+23)] (100), 375 [M^++23] (50), 352 [M^++1] (25); ESIMS/MS *m/z* (%) (parent ion: 352): 251 (100); $C_{19}H_{32}N_2O_4$ (352.47): calcd. C, 64.74; H, 9.15; N, 7.95. Found: C, 64.68; H, 9.03; N, 7.98.

4.4.5. 1-*tert*-Butoxycarbonylamino-2-methyl-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrole-3-carboxylic acid ethyl ester 5e. Purified by flash chromatography (PE/EtOAc, 7:3); clear oil; R_f (20% EtOAc/PE) 0.35; IR (cm^{-1}): 3230, 1746, 1698, 1672; ^1H NMR (500 MHz) ($CDCl_3$) δ 1.30 (t, 3H, CH_3, ^3J=7.3 Hz), 1.48 (s, 9H, $CH_3)_3$), 2.30–2.40 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.61 (five lines, 2H, CH_2, ^3J=6.6 Hz), 2.61 (t, 1H, CH_2, ^3J=6.6 Hz), 2.77 (t, 1H, CH_2, ^3J=6.6 Hz), 4.21 (q, 2H, CH_2O, ^3J=7.3 Hz), 6.89 (br s, 1H, NH, D_2O-exch.). ^{13}C NMR (125 MHz) ($CDCl_3$) δ 9.9, 13.7, 23.7, 26.2, 27.0, 27.4, 58.4, 81.7, 106.8, 125.5, 136.2, 139.3, 154.0, 165.7. APCI-MS *m/z* (%): 309 [M^++1] (100); APCI-MS/MS *m/z* (%): 253 (100); $C_{16}H_{24}N_2O_4$ (308.37): calcd. C, 62.32; H, 7.84; N, 9.08. Found: C, 62.15; H, 7.76; N, 8.97.

4.4.6. 1-*tert*-Butoxycarbonylamino-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylic acid ethyl ester 5f. Purified by flash chromatography (PE/EtOAc, 8:2); clear oil; R_f (10% EtOAc/PE) 0.27; IR (cm^{-1}): 3230, 1748, 1698, 1672; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, CH_3, ^3J=7.0 Hz), 1.50 (s, 9H, $CH_3)_3$), 1.66–1.82 (m, 4H, CH_2), 2.35–2.43 (m, 5H, CH_3, CH_2), 2.60–2.70 (m, 2H, CH_2), 4.22 (q, 2H, CH_2O, ^3J=7.0 Hz), 6.85 (br s, 1H, NH, D_2O-exch.). ^{13}C NMR (125 MHz) ($CDCl_3$) δ 10.3, 14.5, 20.6, 22.6, 23.1, 23.4, 28.1, 59.0, 82.1, 108.3, 116.7, 128.0, 135.8, 154.0, 166.2. ESIMS *m/z* (%): 345 [M^++23] (100); $C_{17}H_{26}N_2O_4$ (322.4): calcd. C, 63.33; H, 8.13; N, 8.69. Found: C, 63.25; H, 8.02, N, 8.81.

4.4.7. 1-*tert*-Butoxycarbonylamino-2-methyl-1,4,5,6,7,8-hexahydro-cyclohepta[*b*]pyrrole-3-carboxylic acid ethyl ester 5g. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (10% EtOAc/PE) 0.28; IR (cm^{-1}): 3277, 1748, 1692, 1672; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, CH_3, ^3J=7.0 Hz), 1.48 (s, 9H, $CH_3)_3$), 1.58–1.83 (m, 6H, CH_2), 2.36 (s, 3H, CH_3), 2.54 (t, 2H, CH_2, ^3J=5.5 Hz), 2.85–2.98 (m, 2H, CH_2), 4.23 (q, 2H, CH_2O, ^3J=7.0 Hz), 6.87 (br s, 1H, NH, D_2O-exch.). ^{13}C NMR (125 MHz) ($CDCl_3$) δ 10.4, 13.7, 23.9, 24.6, 26.2, 27.4, 27.5, 30.8, 58.5, 81.6, 108.8, 121.2, 131.6, 134.2, 153.9, 166.2. APCI-MS *m/z* (%): 337 [M^++1] (100), 281 (35), 237 (25); APCI-MS/MS *m/z* (%) (parent ion: 337): 281 (100); $C_{18}H_{28}N_2O_4$ (336.4): calcd. C, 64.26; H, 8.39; N, 8.33. Found: C, 64.17; H, 8.27, N, 8.45.

4.4.8. 3-*tert*-Butoxycarbonylamino-2-methyl-4,5-dihydro-3*H*-benz[*e*]indole-1-carboxylic acid ethyl ester 5h. Purified by flash chromatography (PE/EtOAc, 95:5); clear oil; R_f (10% EtOAc/PE) 0.35; IR (cm^{-1}): 3282, 1748, 1702, 1676; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, CH_3, ^3J=7.0 Hz), 1.53 (s, 9H, $CH_3)_3$), 2.48 (s, 3H, CH_3), 2.80–2.88 (m, 2H, CH_2,), 2.92–3.01 (m, 2H, CH_2), 4.28 (q, 2H, CH_2O, ^3J=7.0 Hz), 6.98 (br s, 1H, NH, D_2O-exch.), 7.02–7.22 (m, 3H, arom), 7.49 (d, 1H, arom, ^3J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 10.8, 14.7, 21.5, 28.4, 30.4, 59.7, 82.9, 108.9, 119.7, 121.1, 125.7, 126.6, 127.2, 128.4, 128.5, 136.1, 139.2,

153.8, 166.0. ESIMS *m/z* (%): 393 [M^++23] (100), 371 [M^++1] (40); ESIMS/MS *m/z* (%) (parent ion: 371): 315 (100); $C_{21}H_{26}N_2O_4$ (370.44): calcd. C, 68.09; H, 7.07; N, 7.56. Found: C, 67.88; H, 6.91, N, 7.66.

4.4.9. 2-*tert*-Butoxycarbonylamino-1-hydroxy-3-methyl-2-aza-spiro[4.5]dec-3-ene-4-carboxylic acid ethyl ester 5i. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (20% EtOAc/PE) 0.43; IR (cm^{-1}): 3434, 3306, 1712, 1682, 1654, 1602; ^1H NMR ($CDCl_3$) δ 1.15–1.50 (m, 4H, CH_2), 1.28 (t, 3H, CH_3, ^3J=7.3 Hz), 1.47 (s, 9H, $(CH_3)_3$), 1.55–1.80 (m, 4H, CH_2), 1.82–1.98 (m, 1H, CH_2), 2.12 (s, 3H, CH_3), 2.18–2.32 (m, 1H, CH_2), 2.96 (d, 1H, OH, ^3J=8.2 Hz, D_2O-exch.), 4.08–4.20 (m, 2H, CH_2O), 4.91 (d, 1H, CH, ^3J=8.2 Hz), 6.61 (br s, 1H, NH, D_2O-exch.); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.6, 23.0, 24.5, 25.6, 27.8, 28.4, 32.1, 48.5, 59.1, 82.0, 91.8, 106.5, 156.6, 156.9, 166.6. ESIMS *m/z* (%): 377 [M^++23] (100); ESIMS/MS *m/z* (%): 320 (50), 302 (65), 276 (30), 259 (100); $C_{18}H_{30}N_2O_5$ (354.44): calcd. C, 61.00; H, 8.53; N, 7.90. Found: C, 60.97; H, 8.48, N, 7.93.

4.4.10. 1-*tert*-Butoxycarbonylamino-5-hydroxy-2,4,4-trimethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester 5j. Purified by flash chromatography (PE/EtOAc, 9:1); white solid; mp 122–124 °C; R_f (20% EtOAc/PE) 0.25; IR (cm^{-1}): 3426, 3290, 1727, 1713, 1660, 1606; ^1H NMR (300 MHz) CD_3COCD_3 δ 1.18 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.26 (t, 3H, CH_3, ^3J=7.1 Hz), 1.45 (s, 9H, $(CH_3)_3$), 2.10 (s, 3H, CH_3), 2.25 (m, 1H, CH_2), 2.90 (br s, 1H, OH, D_2O-exch.), 4.11 (q, 2H, CH_2O, ^3J=7.1 Hz), 4.75 (s, 1H, CH), 8.12 (br s, 1H, NH, D_2O-exch.); ^{13}C NMR (75 MHz) CD_3COCD_3 δ 11.8, 14.4, 19.2, 26.2, 27.9, 43.4, 58.4, 80.4, 95.2, 107.3, 155.6, 157.8, 166.1. ESIMS *m/z* (%): 315 [M^++1] (100); ESIMS/MS *m/z* (%): 273 (100); $C_{15}H_{26}N_2O_5$ (314.38): calcd. C, 57.31; H, 8.34; N, 8.91. Found: C, 57.23; H, 8.25, N, 8.93.

4.5. 1,4-Dihydro-pyridazine-4-carboxylic acid ethyl esters 6a,b

To a well stirred solution of 5,6-dihydro-4*H*-pyridazines **4a**,**b** (0.5 mmol) in ethanol (2 ml), 250 mg of Amberlyst 15 was added. Stirring was continued until no more starting compound was detectable by TLC, then the solvent was removed under vacuum and the crude purified by flash chromatography eluting with PE/EtOAc mixtures.

Compounds **6a**,**b** are quite unstable thus giving rise to isomerization and decomposition phenomena during ^{13}C NMR acquisition, so only proton spectra are reported for these derivatives.

For same reasons elemental analyses are out of the accepted range of accuracy and are not given. Thus, whereas the identity of these compounds can be easily detected by proton NMR and MS spectra, no data are available to verify their purity grade.

4.5.1. 3-Methyl-5-phenyl-2,5-dihydro-pyridazine-4-carboxylic acid ethyl ester 6a. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (10% EtOAc/PE) 0.22; IR (cm^{-1}): 3327, 1731, 1693, 1612; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, CH_3, ^3J=7.0 Hz), 2.33 (s, 3H, CH_3), 4.08 (q, 2H, CH_2O, ^3J=7.0 Hz), 4.53 (d, 1H, CH-5, ^3J=4.0 Hz), 6.91 (br s, 1H, NH, D_2O-exch.), 7.25–7.50 (m, 6H, arom, =CH-6); ESIMS *m/z* (%): 265 [M^++23] (40), 244 [M^++1] (100), 215 (80); ESIMS/MS *m/z* (%) (parent ion 244): 215 (100).

4.5.2. 5-Isopropyl-3-methyl-2,5-dihydro-pyridazine-4-carboxylic acid ethyl ester 6b. Purified by flash chromatography (PE/EtOAc, 9:1); clear oil; R_f (20% EtOAc/PE) 0.26; IR (cm^{-1}): 3339, 1694, 1677, 1618; ^1H NMR ($CDCl_3$) δ 0.83 and 0.88 (d, 3H, CH_3, ^3J=6.8 Hz), 1.21 (t, 3H, CH_3, ^3J=7.0 Hz), 1.66 (eight lines, 1H, CH, ^3J=6.8 Hz), 2.27 (s, 3H, CH_3), 3.27 (dd, 1H, CH-5, ^3J=6.8, 4.4 Hz), 4.14 (q, 2H, CH_2O, ^3J=7.0 Hz), 6.80 (d, 1H, CH-6, ^3J=4.4 Hz), 7.25 (br s, 1H, NH, D_2O-exch); ESIMS *m/z* (%): 233 [M^++23] (40), 211 [M^++1] (100), 170 (30); ESIMS/MS *m/z* (%) (parent ion 211): 170 (100), 124 (50).

4.6. Crystal structure determination of 4a

Air stable, colorless crystals of **4a** suitable for X-ray diffraction were obtained by slow evaporation from a dichloromethane solution.

A prismatic single crystal of the compound was mounted on a glass fiber at a random orientation, on a Bruker SMART CCD diffractometer. The data collection was performed at 293 K by the ω-scan method, in the interval $2<\theta<25°$. The space group was determined from the systematic absences, while the cell constants were refined, at the end of the data collection with the data reduction software SAINT.[11] The collected intensities were corrected for Lorentz and polarization factors and empirically for absorption using the SADABS program.[12] The structures were solved by direct methods (SIR97)[13] and refined by full-matrix, least-squares on F^2 (SHELXL-97[14] and WINGX programs[15]) using anisotropic displacement parameters for all atoms except for the hydrogen atoms.

The two hydrogens bounded to C(21) atom were included in the refinement in calculated positions and refined using a riding model ($B(H)=1.2\times B(C_{bonded})(Å^2)$), while all the other hydrogens were located from a Fourier Difference Map and refined applying a constrain on their isotropic displacements.

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