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Synthesis and subsequent reactivity of 1-amino-2-aza-1,3-butadienes derived from β-amino esters

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Abstract—A high yield preparation of 1-amino-2-aza-1,3-butadienes derived from β-amino esters from *N*-unsubstituted amidines and acetylenic esters is described. These substrates are efficient starting material for the preparation of dihydrotriazines and 5-amino pyrrolidin-3-ones.

1. Introduction

Functionalized 2-azabutadiene systems have proved to be efficient key intermediates in organic synthesis for the preparation of heterocycles,[1,2] and the presence of electron-donating groups in these substrates favour their reactivity with electron-deficient dienophiles.[1–3] In this context, we have been involved in the design of new strategies for the preparation of three,[4] five[5] and six[6] nitrogen heterocyclic compounds as well as in the synthesis of 1-aza[7] **I** (Fig. 1) or 1,2-diaza-1,3-butadienes **II**.[8] Likewise, we described the preparation of functionalized 2-azadiene systems **III** (Fig. 1)[9] and electron-poor 2-aza-1,3-butadienes derived from amino esters[10] and their use in the preparation of heterocyclic compounds.[9,10]

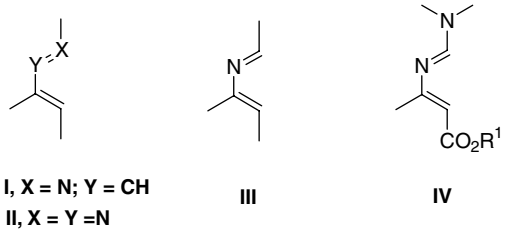
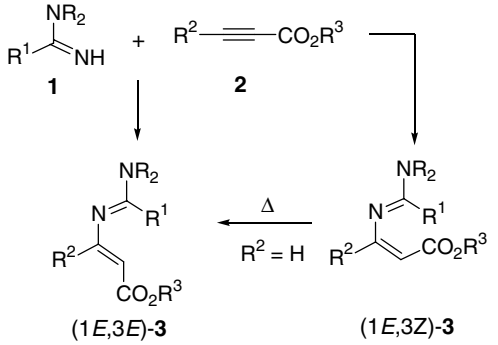


Figure 1.

The synthetic interest of electron-rich 2-azadienes[3,11] and a recent publication[12] reporting the cyclocondensation of *N*-substituted amidines with dimethyl acetylenedicarboxylate to give 1-substituted-5-dialkylamino-4-pyrrolin-3-ones prompted us to report our own results concerning a high yield synthesis of a new family of 1-amino-2-aza-1,3-butadienes **IV** (Fig. 1) from *N*-unsubstituted amidines[13] and acetylenic esters and their use for the preparation of five and six membered heterocycles.

2. Results and discussion

1-Amino-2-azadienes **3a–e** (R^1 = Me, Ph) were obtained with excellent yields through a conjugated addition of amidines **1** to acetylenic esters **2** (Scheme 1, Table 1,



Scheme 1.

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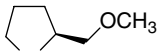
Table 1. 2-Aza-1,3-butadienes **3**, dihydrotriazines **5** and 5-aminopyrrolidin-3-ones **8**, **10** and **11** obtained

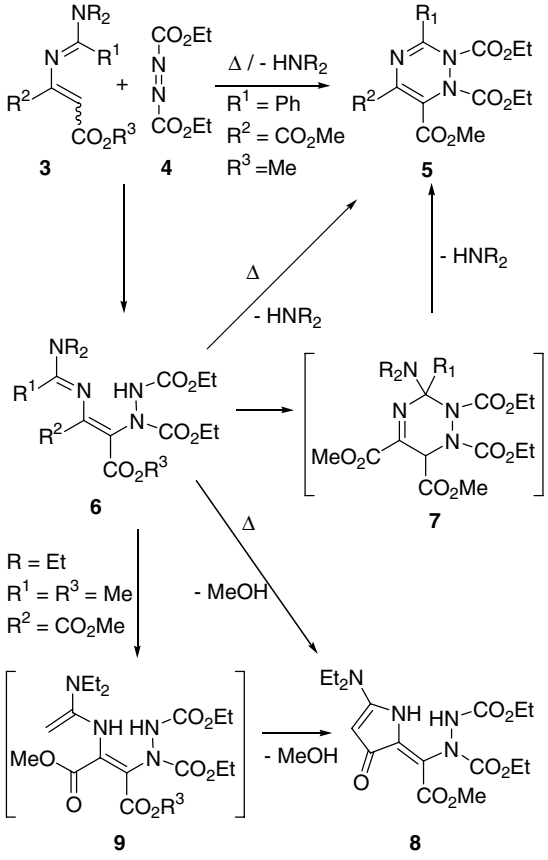
Entry	Compound	R	R^1	R^2	R^3	Reaction conditions			Yield (%)	3*E*/3*Z* (%)	Mp (°C)
						T (°C)	Time (h)	Solvent			
1	**3a**	Et	Me	CO_2Me	Me	−10	4	$CHCl_3$	97[a]	100/0	Oil
2	**3b**	$-(CH_2)_5-$	Me	CO_2Me	Me	−15	2	$CHCl_3$	95[a]	100/0	Oil
3	**3c**	$-(CH_2)_5-$	Ph	CO_2Me	Me	−15	5	$CHCl_3$	99[a]	0/100	Oil
4	**3d**	Et	Me	H	Et	20	24	$CHCl_3$	98[a]	20/80	Oil
5	**3e**	$-(CH_2)_5-$	Me	H	Et	20	24	$CHCl_3$	95[a]	35/65	Oil
6	**3f**		Me	CO_2Me	Me	−15	4	$CHCl_3$	90[b]	100/0	Oil
7	**5a**	Et	Me	CO_2Me	Me	110	72	Toluene	6[b]	—	Oil
8	**5c**	$-(CH_2)_5-$	Ph	CO_2Me	Me	60	24	$CHCl_3$	56[b]	—	Oil
9	**6a**	Et	Me	CO_2Me	Me	60	72	$CHCl_3$	34[b]	—	Oil
10	**8**	—	—	—	—	110	72	Toluene	56[b]	—	Oil
11	**10a**	Et	—	—	—	140	24	Xylene	73[b]	—	167–168
12	**10b**	$-(CH_2)_5-$	—	—	—	140	24	Xylene	66[b]	—	164–165
13	**11**		—	—	—	25	15	$CHCl_3$	48	—	Oil

[a] Percentage of consumption of the starting material by NMR analysis of the crude reaction mixture.
[b] Yield of isolated compounds by column chromatography.

entries 1–5). 1-Amino-2-azadienes **3a–e** were unstable to distillation or chromatography and therefore were not isolated and used in situ for the following reactions. The presence of the non isolable compounds was established on the basis of the spectroscopic data of their crude reaction mixtures.[14,15] The isomerization of *E*,*Z* towards *E*,*E* isomer was observed when a solution of *E*,*Z* isomer of **3d** or **3e** was heated at 60 °C in $CHCl_3$. Similar isomerizations of 2-azadienes derived from β-amino esters have been observed previously.[16] The scope of this process is not restricted to the use of achiral alkyl and aryl amidines **1** (R^1 = Me, Ph), given that optically active amidine derived from (*S*)-2-methoxymethylpyrrolidine gave only optically active *E*,*E*-1-amino-2-azadiene **3f** (Scheme 1, Table 1, entry 6).

Then, the synthetic usefulness of the new 1-amino-2-azadienes **3** as key intermediates in organic synthesis and especially in the preparation of heterocyclic derivatives was explored. Amino substituted 2-azadiene **3c** containing an aryl group (R^1 = Ph) reacted with diethyl azodicarboxylate **4** in refluxing $CHCl_3$ to give six membered heterocyclic compound **5c**[17] (Scheme 2, Table 1, entry 8). The structure of compound **5c** was assigned on the basis of the 1D and 2D NMR spectroscopy, including HMQC and HMBC experiments and mass spectral data. The mass spectrometry of **5c** showed the molecular ion peak (*m*/*z* 419). The formation of compound **5c** could be explained either by a concerted [4+2] Aza-Diels–Alder (ADA) process with formation of cycloadduct **7** followed by the loss of amine (HNR_2), or through addition of the enamine moiety of azadiene **3** to azoester **4** to give acyclic compounds **6** followed by its intramolecular addition of the NH to the amidine group with the formation of cycloadduct **7** and the subsequent loss of amine (HNR_2).

In order to test the pathway of the process, we try to trap the acyclic **6** or cyclic intermediate **7**. Thus, the treatment of compound **3a** ($R^1 = R^3$ = Me, $R^2 = CO_2Me$) in refluxing $CHCl_3$ with diethyl azodicarboxylate **4** afforded the acyclic derivative **6a** (Scheme 2, Table 1, entry 9). Moreover, we have also observed that heating acyclic compound **6a** in refluxing toluene compounds **5a** (6%) and **8** (56%) were obtained (Scheme 2, Table 1, entries 7 and 10). The structure of compounds **5a** was established by comparison with dihydrotriazine **5c** (vide supra). On the other hand, the structure of compound **8** (Scheme 2) was assigned on the basis of

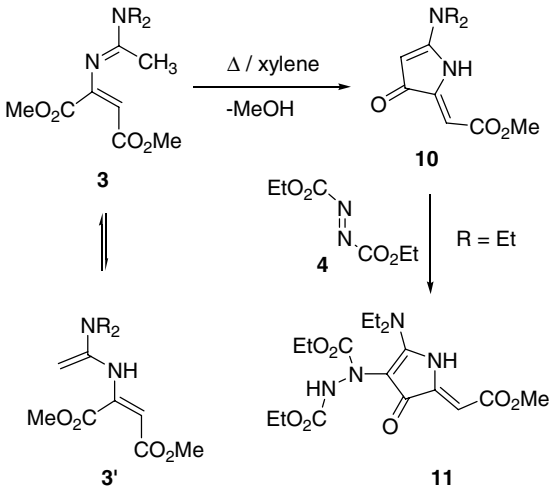


Scheme 2.

the 1D and 2D spectroscopy, including NOESY-1D, HMQC and HMBC experiments and mass spectral data. The ^{1}H NMR spectrum of compound **8** showed a singlet at 3.88 ppm for three hydrogens of OMe group, one singlet at 4.71 ppm for the cyclic enaminic hydrogen bonded to C-4. The ^{13}C NMR spectrum of **8** showed the disappearance of one carboxylate group from the precursor acyclic derivative **6** and the appearance of one signal at 179.7 ppm corresponding to a carbonyl group.

The formation of compound **5a** could be explained by the intramolecular addition of the NH to the amidine group of acyclic compounds **6** to give cycloadduct **7** followed by the loss of amine (HNR_2). However, the formation of compound **8** involves the enaminic tautomer form **9** of compound **6a** which cyclizes by intramolecular cyclocondensation to compound **8** with the loss of MeOH. This heterocyclic compound **8** contains the 5-dialkylamino-4-pyrrolin-3-one skeleton, and it is noteworthy that these compounds are very important substrates for the preparation of biologically active tetramic acid derivatives[18] and antibiotics.[19]

With these results in hand and with the objective of obtaining simple 5-amino-4-pyrrolin-3-ones, we performed the thermal treatment of 1-amino-2-azadienes **3a**,**b** ($R^1 = R^3 = CH_3$, $R^2 = CO_2Me$) in xylene at 140 °C in a sealed tube to give cyclic derivatives **10a**,**b** directly (Scheme 3, Table 1, entries 11 and 12). The formation of compounds **10** could be explained by the intramolecular cyclization of the enaminic tautomer **3'** of compounds **3** ($R^1 = CH_3$) and the loss of methanol. The structure of compounds **10** was assigned on the basis of 1D and 2D spectroscopic data.[20] HOESY ^{1}H–^{13}C experiment for compound **10a** showed a cross signal between the hydrogen atom of amino group and carboxylate carbon atom, which suggests an hydrogen bridge bonding between amino and carboxylate groups. Moreover the IR spectra of compound **10a** showed a signal corresponding to a frequency associated with an amino group at 3409 cm^{-1} which does not change with sample dilution (0.5 M, 0.25 M, 0.12 M in $CHCl_3$). This result is consistent with the presence of the hydrogen bridge bonding between the hydrogen atom of the amino group and the oxygen atom of the carboxylic group, which indicates the *Z* configuration of exocyclic double bond.



Scheme 3.

5-Amino-4-pyrrolin-3-ones **10** are multifunctional compounds containing two enamines, an enaminone and a secondary enamino ester. Then, the regioselective enaminone character (reaction through the C-4) versus the enamino ester reactivity (reaction through the exocyclic carbon) was explored by the reaction of compound **10a** with diethyl azodicarboxylate **4** at room temperature in $CHCl_3$, and only adduct **11** (Scheme 3, Table 1, entry 13) was obtained in a regioselective fashion. The formation of this compound can be explained by the nucleophilic addition of C-4 (enaminone moiety) of 5-amino-1,2-dihydropyrrol-3-one ring of **10a** to the electrophilic nitrogen of diethyl azodicarboxylate. Compound **11** was characterized by its spectroscopic data. Thus, ^{1}H NMR spectroscopic data showed the disappearance of the signal at around 4.7 ppm corresponding to the cyclic enaminic proton, while the signal at 5.79 ppm corresponding to exocyclic enaminic proton remained. The mass spectrometry of compound **11** showed a molecular ion (*m*/*z* 398, 6%).

In conclusion, 1-amino-2-azadienes derived from β-amino esters can be prepared readily with very high yields by conjugated addition of *N*-unsubstituted amidines to acetylenic compounds. These substrates react with azoesteres to afford acyclic and heterocyclic compounds. Moreover, the substituted 1-amino-2-azadienes containing a carboxylate group in position 3 cyclize to give 5-amino-4-pyrrolin-3-ones. The new family of 1-amino-2-azadienes derived from β-amino esters may be important synthons in organic synthesis and in the preparation of acyclic derivatives heterocycles,[1–3] while the preparation of 5-dialkylamino-4-pyrrolin-3-one derivatives may open a new way for the preparation of biologically active tetramic acid derivatives.[18,19]

Acknowledgements

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References and notes

1. For reviews see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698; (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471; (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
2. For recent contributions, see: (a) Bongini, A.; Panunzio, M.; Tamanini, E.; Martelli, G.; Vicennati, P.; Moneri, M. *Tetrahedron: Asymmetry* **2003**, *14*, 993–998; (b) Alves, M.

J.; Duraes, M. M.; Gil, A. *Tetrahedron Lett.* **2003**, *44*, 5079–5082; (c) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed* **2002**, *41*, 1941–1945; (d) Moody, C. J.; Hughes, R. A.; Thompson, S. P.; Alcaraz, L. *Chem. Commun.* **2002**, 1760–1761; (e) Ntirampebura, D.; Ghosez, L. *Synthesis* **2002**, 2043–2052.

3. (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617–2618; (b) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Synlett* **1999**, 1735–1738; (c) Ntirampebura, D.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 7079–7082; (d) Ghosez, L. *Pure Appl. Chem.* **1996**, *68*, 15–22.
4. (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2005**, *70*, 8895–8901; (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron* **2004**, *60*, 8937–8947.
5. (a) Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, 2843–2850; (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2541–2552.
6. (a) Palacios, F.; Aparicio, D.; Lopez, Y.; de los Santos, J. M.; Alonso, C. *Eur. J. Org. Chem.* **2005**, 1142–1147; (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Lopez de Munain, R.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005**, *61*, 1087–1094; (c) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; López de Munain, R. *Org. Lett.* **2002**, *4*, 2405–2408.
7. (a) Palacios, F.; Aparicio, D.; Lopez, Y.; de los Santos, J. M.; Ezpeleta, J. M. *Tetrahedron* **2006**, *62*, 1095–1102; (b) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767–8774.
8. Palacios, F.; Aparicio, D.; Lopez, Y.; de los Santos, J. M. *Tetrahedron* **2005**, *61*, 2815–2830.
9. (a) Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2005**, *61*, 2779–2794; (b) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941–1946; (c) Palacios, F.; Alonso, C.; Rubiales, G. *J. Org. Chem.* **1997**, *62*, 1146–1154.
10. (a) Palacios, F.; Herrán, E.; Rubiales, G.; Ezpeleta, J. M. *J. Org. Chem.* **2002**, *67*, 2131–2135; (b) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 3497–3500.
11. Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15644–15651.
12. Erden, I.; Ozer, G.; Hoarau, C.; Cao, W. *J. Heterocycl. Chem.* **2006**, *43*, 395–399.
13. Rousselet, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 6395–6398.
14. Spectroscopic data for compound *E*,*E*-(**3a**): IR (KBr) ν: 1719, 1584 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, $^3J_{HH} = 7.2$ Hz, 6H), 1.89 (s, 3H), 3.42 (m, 4H), 3.65 (s, 3H), 3.78 (s, 3H), 6.04 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3 (m), 15.5, 42.7, 50.7, 52.4, 103.1, 151.0, 157.3, 166.4, 166.8. MS (EI) *m*/*z* (%): 256 (M^+, 10).
15. Compounds **3a**,**b** were obtained only as the *E*,*E*-isomers, compound **3c** only as the *E*,*Z*-isomer, while compounds **3d**,**e** were obtained as a mixture of *E*,*E* and *E*,*Z* isomers.
16. Palacios, F.; Alonso, C.; Rubiales, G.; Villegas, M. *Tetrahedron* **2005**, *61*, 2779–2794.
17. Data for compound **5c**: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, $^3J_{HH} = 7.2$ Hz, 6H), 3.62 (s, 6H), 4.21 (t, $^3J_{HH} = 7.2$ Hz, 4H), 7.34–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 51.3, 62.3, 127.5–132.8 (m), 155.0, 156.0, 162.5, 162.8, 164.8, 166.4, 170.8. MS (CI) *m*/*z*: 420 (M^++1, 30).
18. For reviews about bioactive tetramic acid derivatives see: (a) Huang, P.-Q. *Synlett* **2006**, 1133–1149; (b) Ghisalberti, E. L. In *Studies in Natural Products Chemistry, Bioactive Natural Products (Part I)*; Elsevier, 2003; Vol. 28, pp 109–163; (c) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981–2001.
19. For recent contributions about tetramic acid antibiotics see: (a) Iwata, Y.; Maekawara, N.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1532–1536; (b) Segeth, M. P.; Bonnefoy, A.; Bronstrup, M.; Knauf, M.; Schummer, D.; Toti, L.; Vetrtesy, L.; Wetzel-Raynal, M. C.; Wink, J.; Seibert, G. *J. Antibiot.* **2003**, *56*, 114–122; (c) Michael, A. P.; Grace, E. J.; Kotiw, M.; Barrow, R. A. *J. Nat. Prod.* **2002**, *65*, 1360–1362; (d) Holtzel, A.; Ganzle, M. G.; Nicholson, G. J.; Hammes, W. P.; Jung, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2766–2768.
20. Data for compound **10a**: Dark brown crystals, mp 167–168 °C, R_f (10/1, ethyl acetate/methanol): 0.33. IR (KBr) ν: 3393, 1661, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, $^3J_{HH} = 7.1$ Hz, 6H), 3.41 (q, $^3J_{HH} = 7.1$ Hz, 4H), 3.77 (s, 3H), 4.64 (s, 1H), 5.80 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.0, 14.1, 43.5, 45.9, 51.7, 80.6, 91.4, 149.5, 166.0, 169.8, 180.9; MS (EI) *m*/*z* 224 (M^+, 10).