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Aminovinyl ketones and aminovinyl esters as C–C–N building blocks for the synthesis of 1*H*-pyrrolo[3,2-*e*]1,2,4-triazines

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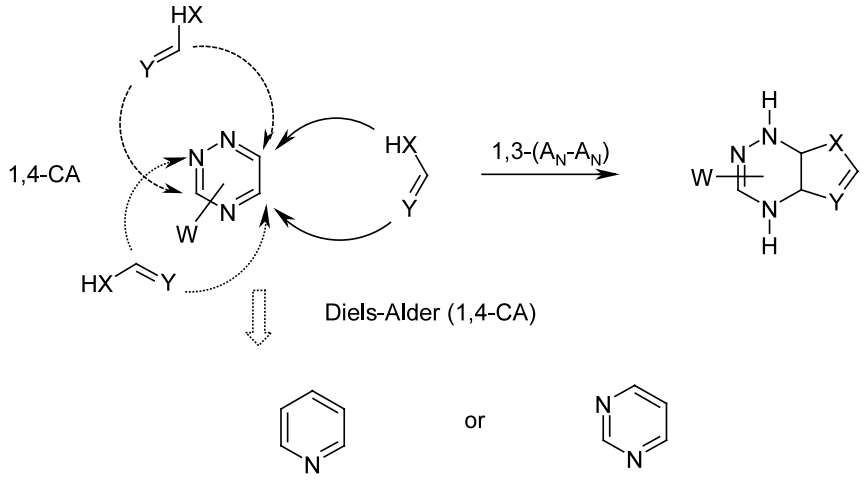
Dedicated to academician G. A. Tolstikov on the occasion of his 70th birthday

Abstract—5,6-Unsubstituted-3-aryl-1,2,4-triazines were found to react with aminovinyl ketones and aminovinyl esters in acetic anhydride to form derivatives of 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]1,2,4-triazines in good yields.

We have previously reported that the tandem di-addition (A_N–A_N) or 'addition–substitution' (A_N-S_N^{ipso}) reactions of 1,2,4-triazines and their quaternary salts with 1,3-bifunctional reagents (CH-active amides, ketene-*N*,*N*-aminals or thioamides) provide efficient approaches to condensed triazines.[1–8] In spite of the fact that the chemistry of 1,2,4-triazines has been extensively studied,[9–13] the reactivity of this system towards bifunctional electron-rich unsaturated reagents is still quite unpredictable. Indeed, 1,2,4-triazines are known to undergo 1,4-cycloaddition reactions (1,4-CA) with enamines and other electron-rich dienophiles according to the scheme of inverse electron demand Diels–Alder reactions in which triazines are transformed into pyridines or pyrimidines (Scheme 1).[14,15]

On the other hand, enamines are 1,3-*C*,*N*-bifunctional reagents and, taking into account that activated forms of 1,2,4-triazines are able to undergo the tandem A_N–A_N and A_N–S_N^{ipso} reactions with bifunctional



Scheme 1.

Keywords: 1,2,4-triazines; tandem di-addition reactions; aminovinyl ketones; aminovinyl esters.
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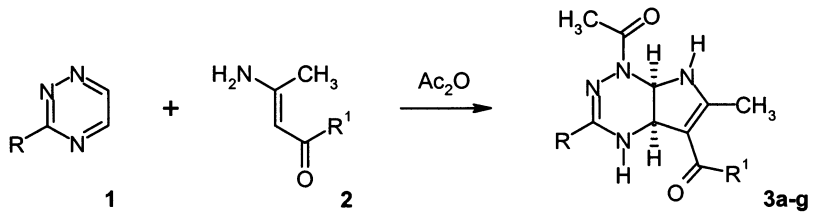

a: R= Ph, R^1= OEt; **b**: R= *p*-MeO-C_6H_4, R^1= OEt; **c**: R= *p*-NO_2-C_6H_4, R^1= OEt;
d: R= SCH_2Ph, R^1= OEt; **e**: R= Ph, R^1= Me; **f**: R= R^1= Ph; **g**: R= SC_2H_5, R^1= OEt.

Scheme 2.

nucleophiles at C-5 and C-6, one might expect the formation of condensed 1,2,4-triazines. Since several patterns of chemical behaviour of 1,2,4-triazines are possible, finding appropriate reagents and conditions for a particular reaction pathway is a good task for chemists.

In this paper we wish to describe the reaction of 1,2,4-triazines with enamines in which the reactivity of the C=C double bond is reduced by electron-withdrawing substituents. We have found that the reaction of 5,6-unsubstituted-3-aryl-1,2,4-triazines **1** with aminovinyl ketones and aminovinyl esters **2** in acetic anhydride proceeds regioselectively and smoothly at room temperature resulting in the formation of pyrrolo[3,2-*e*]1,2,4-triazines **3a**–**g** (Scheme 2).

Evidence for the structures of **3a**–**g** was provided by ^1H and ^{13}C NMR, including two-dimensional ^1H–^{13}C NMR performed with proton-decoupling experiments, HETCOR and HMBC procedures and by mass spectroscopy. The data of elemental analyses and peaks of molecular ions (M^+) in the mass spectra of compounds **3a**–**g** are in a full agreement with the 1:1 adduct formation (Table 1). Unequivocal assignments of signals in the ^1H NMR spectra of pyrrolo[3,2-*e*]1,2,4-triazines **3a**–**g** were made on the basis of two-dimensional 2D NOESY experiments. Indeed, the signal of N^4-H was identified due to cross-peaks with the *ortho*-protons of the aryl substituent at C-5 and the ring junction proton 3a-H, while N^1-H of the pyrrole ring gives rise to cross-peaks with 7a-H and the methyl group protons at 2-C (Fig. 1). These data allow the regio-orientation of the pyrrole ring and the position of the *N*-acetyl group to be established. It is worth noting that intramolecular O···H hydrogen bonds between the two NH protons and the two acetyl groups appear to contribute towards stabilization of cycloadducts with such regio-orientation (Table 2).

The ring junction proton 3a-H appears as a double doublet (4.4–4.9 ppm) with ^3J(3a-H, 7a-H) = 8.2–8.8 Hz and ^3J(3a-H, N^4-H) = 1.0 Hz, while proton 7a-H resonates as a double doublet (5.9–6.0 ppm) with ^3J(7a-H, N^1-H) = 8.2–8.8 Hz and an additional coupling with the NH proton ^3J(7a-H, N^1-H) = 1.5 Hz. The values of the vicinal coupling constants ^3J(7a-H, 3a-H) = 8.2–8.8 Hz correspond to the *cis*-orientation of the ring junction protons, which is a common feature for tetrahydropyrazines and tetrahydro-1,2,4-triazines condensed with five-membered heterocycles.[16]

In the ^{13}C NMR spectrum of **3c** the ring junction carbon atoms 3a-C and 7a-C were observed at 51.51 and 62.66 ppm, while C-2, C-3 and C-5 carbon resonance signals were registered at 146.03, 98.56 and 161.48, respectively, which is in good agreement with the structure.

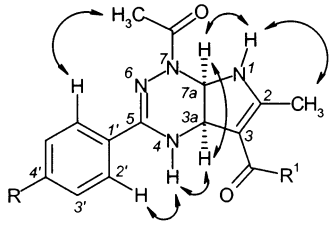

Figure 1. Selected ^1H–^1H NOESY cross peaks found in **3a**,**c**.

Table 1. Melting point, yields and elemental analyses data for compounds **3a**–**g**

Compound	Mp (°C)	Found (%)			Formula	Calculated			Yield (%)
		C	H	N		C	H	N	
3a	162–163	61.94	5.96	17.14	$C_{17}H_{20}N_4O_3$	62.18	6.14	17.06	59
3b	190–192	60.28	6.10	15.63	$C_{18}H_{22}N_4O_4$	60.32	6.19	15.63	58
3c	236–238	54.53	4.95	18.54	$C_{17}H_{19}N_5O_5$	54.69	5.13	18.76	18
3d	144–145	57.88	5.91	14.86	$C_{18}H_{22}N_4O_3S$	57.74	5.92	14.96	54
3e	215–217	64.45	6.04	18.77	$C_{16}H_{18}N_4O_2$	64.41	6.08	18.78	49
3f	199–201	69.93	5.64	15.54	$C_{21}H_{20}N_4O_2$	69.98	5.59	15.54	50
3g	142–143	49.92	6.40	17.93	$C_{13}H_{20}N_4O_3S$	49.98	6.45	17.93	13

Table 2. ^{1}H NMR spectral data for pyrrolo[3,2-*e*]1,2,4-triazines **3a–g** in DMSO-d_6/CCl_4

Compound	^{1}H chemical shifts (ppm) and coupling constants (Hz)						
	$COCH_3$	CH_3	R^1	H-3a	H-7a	N^4-H N^1-H	R
3a[a]	2.27 (s, 3H)	2.07 (s, 3H)	1.27 (t, 3H, $OCH_2C\underline{H}_3$, $J=7.1$) 4.10 (k, 2H, $OC\underline{H}_2CH_3$, $J=7.1$)	4.61 (d, $J=8.6$)	6.03 (dd, $J=8.6$, 1.5)	6.69 (br.s) 7.59 (br.s)	7.11 (m, 3H, Ph) 7.4 (m, 2H, Ph)
3b	2.27 (s, 3H)	2.06 (s, 3H)	1.27 (t, 3H, $OCH_2C\underline{H}_3$, $J=7.0$) 4.09 (k, 2H, $OC\underline{H}_2CH_3$, $J=7.0$)	4.57 (d, $J=8.6$)	5.97 (d, $J=8.6$)	6.31 (br.s) 7.52 (br.s)	3.80 (s, 3H, $C_6H_4OC\underline{H}_3$) 6.89 (d, 2H, $C_6\underline{H}_4OCH_3$, $J=8.9$) 7.60 (d, 2H, $C_6\underline{H}_4OCH_3$, $J=8.9$)
3c[a]	2.30 (s, 3H)	2.08 (s, 3H)	1.24 (t, 3H, $OCH_2C\underline{H}_3$, $J=7.1$) 4.11 (k, 2H, $OC\underline{H}_2CH_3$, $J=7.1$)	4.55 (dd, $J=8.2$, 1.0)	6.00 (dd, $J=8.2$, 1.5)	7.07 (d, $J=1.0$) 7.59 (d, $J=1.5$)	7.99 (d, 2H, $C_6H_4NO_2$, $J=9.1$) 8.22 (d, 2H, $C_6H_4NO_2$, $J=9.1$)
3d	2.14 (s, 3H)	2.08 (s, 3H)	1.22 (t, 3H, $CH_2C\underline{H}_3$, $J=7.1$) 4.05 (k, 2H, $C\underline{H}_2CH_3$, $J=7.1$)	4.36 (d, $J=8.2$)	5.94 (dd, $J=8.2$, 1.5)	6.57 (br.s) 7.45 (br.s)	7.20–7.35 (m, 5H, Ph) 4.14 (m, 2H, SCH_2)
3e	2.29 (s, 3H)	2.14 (s, 3H)	2.14 (s, 3H, CH_3)	4.65 (d, $J=8.6$)	5.99 (dd, $J=8.6$, 1.5)	6.57 (br.s) 7.91 (br.s)	7.36–7.39 (m, 3H, Ph) 7.65–7.69 (m, 2H, Ph)
3f	2.32 (s, 3H)	1.57 (s, 3H)	7.38–7.44 (m, 5H, Ph)	4.85 (d, $J=8.5$)	6.11 (d, $J=8.5$)	6.63 (br.s) 8.26 (br.s)	7.38–7.44 (m, 3H, Ph) 7.66–7.70 (m, 2H, Ph)
3g	2.16 (s, 3H)	2.07 (s, 3H)	1.23 (t, 3H, $CH_2C\underline{H}_3$, $J=7.1$) 3.98–4.11 (m, 2H, $C\underline{H}_2CH_3$, $J=7.1$)	4.40 (d, $J=8.8$)	5.95 (d, $J=8.8$)	6.33 (br.s) 7.44 (br.s)	1.29 (t, 3H, $CH_2C\underline{H}_3$, $J=7.2$) 2.78–3.00 (m, 2H, $C\underline{H}_2CH_3$, $J=7.2$)

[a] Recorded in [$^2H_6$]DMSO.

Conclusion

Thus, we have found that the cyclizations of 1,2,4-triazines **1** with aminovinyl ketones or aminovinyl esters **2** in acetic anhydride lead to 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines. Derivatives of the same heterocyclic system have been obtained earlier through the reactions of 1,2,4-triazines with acetoacetamides and *N*,*N*-keteneaminals.[5,6]

The results obtained demonstrate that aminovinyl ketones and aminovinyl esters are appropriate C–C–N building blocks for the synthesis of 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]1,2,4-triazines. Also, it has been demonstrated that the tandem nucleophilic A_N–A_N di-addition reactions are an effective synthetic tool towards a variety of fused 1,2,4-triazines.

Experimental

^{1}H spectra were recorded in [$^2H_6$]DMSO/CCl_4 solution on a Bruker WP-250 instrument (250 MHz for ^{1}H). The ^{13}C and ^{1}H NMR spectra of **3a**,**c** in [$^2H_6$]DMSO were obtained on a Bruker DRX-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Mass spectra were recorded using a Varian MAT 311A spectrometer.

General procedure for the preparation of 3a–g

The aminovinyl ketone or aminovinyl ester **2** (3.2 mmol) was added to solution or suspension of 3-substituted-1,2,4-triazine **1** (3.21 mmol) in acetic anhydride, depending on the substrate. The reaction mixture was stirred at room temperature for 1 h–2 days. The precipitate obtained was filtered off and washed with a small amount of acetic anhydride, diethyl ether and dried in air.

For 3a: The reaction was carried out in 1 ml of acetic anhydride for 1 h. ^{13}C NMR, δ (ppm) and J_{CH} (Hz): 13.50 (qd, CH_3, $J=128.9$, 1.2), 14.58 (qt, $COOCH_2\underline{C}H_3$, $J=126.4$, 2.5), 21.21 (q, $CO\underline{C}H_3$, $J=128.9$), 51.51 (dd, C-3a, $J=157.1$, 5.2), 58.04 (tq, $COO\underline{C}H_2CH_3$, $J=146.4$, 4.5), 62.80 (d, C-7a, $J=160.9$), 98.22 (m, C-3), 125.96 (ddd, Ph, C-2′, $J=159.9$, 8.3, 6.3), 128.22 (dd, Ph, C-3′, $J=159.2$, 5.4), 129.81 (dt, Ph, C-4′, $J=162.2$, 6.7), 133.56 (t, Ph, C-1′, $J=6.9$), 145.44 (m, C-2), 161.35 (dt, C-5, $J=6.7$, 2.7 Hz), 165.09 (t, $\underline{C}OOCH_2CH_3$, $J=3.1$), 170.36 (qd, $\underline{C}OCH_3$, $J=6.4$, 0.9). MS m/z (I, %): 329 (20, M+1$^+$), 328 (100, M$^+$), 285 (29), 283 (24), 282 (74), 167 (28), 166 (25), 158 (20), 124 (31), 108 (43), 104 (72).

For 3b: The reaction was carried out in 2.5 ml of acetic anhydride for 6 h. MS m/z (I, %): 359 (21, M+1$^+$), 358

(100, M^+), 315 (23), 312 (42), 166 (30), 134 (76), 124 (21), 108 (35).

For 3c: The reaction was carried out in 30.5 ml of acetic anhydride for 2 days. ^{13}C NMR, δ (ppm) and J_{CH} (Hz): 13.54 (qd, CH_3, $J=129.2$, 1.4), 14.56 (qt, $COOCH_2\underline{C}H_3$, $J=126.4$, 2.5), 21.15 (q, $CO\underline{C}H_3$, $J=129.0$), 51.51 (dd, C-3a, $J=157.1$, 5.2), 58.10 (tq, $COO\underline{C}H_2CH_3$, $J=146.4$, 4.5), 62.66 (d, C-7a, $J=160.4$), 98.56 (m, C-3), 123.30 (dd, Ph, C-3′, $J=169.3$, 4.8), 127.38 (dd, Ph, C-2′, $J=165.8$, 7.0), 139.52 (t, Ph, C-1′, $J=7.8$), 143.06 (m, C-2), 147.98 (tt, Ph, C-4′, $J=9.6$, 3.3), 161.48 (m, C-5), 164.94 (t, $\underline{C}OOCH_2CH_3$, $J=2.7$), 170.57 (qd, $\underline{C}OCH_3$, $J=6.4$, 0.8). MS m/z (I, %): 373 (55, M^+), 330 (25), 327 (100), 167 (28), 166 (31), 153 (21), 124 (39), 108 (47), 103 (22).

For 3d: The reaction was carried out in 2.5 ml of acetic anhydride for 6 h. MS m/z (I, %): 374 (51, M^+), 167 (31), 124 (21), 108 (27), 91 (100).

For 3e: The reaction was carried out in 1 ml of acetic anhydride for 1 h. MS m/z (I, %): 298 (100, M^+), 255 (53), 152 (30), 137 (51), 124 (30), 123 (27), 108 (98), 104 (100), 82 (36), 77 (31).

For 3f: The reaction was carried out in 6 ml of acetic anhydride for 24 h. MS m/z (I, %): 360 (86, M^+), 317 (34), 199 (36), 184 (44), 108 (44), 105 (100), 104 (62), 77 (54).

For 3g: The reaction was carried out in 2.5 ml of acetic anhydride for 1 h. MS m/z (I, %): 313 (100, M+1$^+$), 267 (45), 167 (64), 166 (33), 124 (42), 108 (52), 60 (29).

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