2-Aminobuta-1,3-dienes as annulation reagents for 4-quinolones and benzothiopyran-4-ones: an attractive route for the highly diastereoselective synthesis of acridine- and thioxanthene-derivatives

COMMUNICATION

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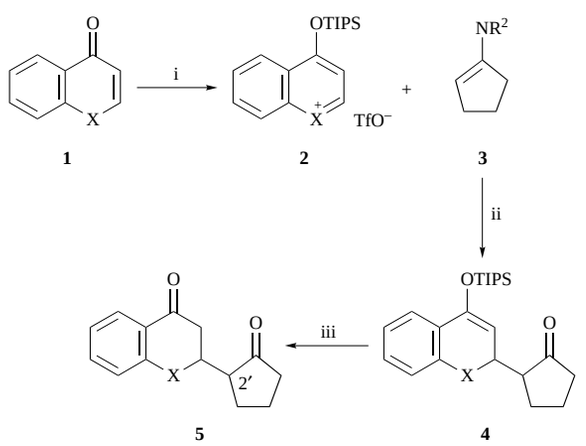
Enamines regioselectively add to the C=N$^+$-bond of 4-silyloxyquinolinium triflates with high yields, and the BF_3·Et_2O mediated annulations of 4-quinolones with 2-aminobuta-1,3-dienes proceed with high diastereoselectivity to give substituted 1,2,3,4,4a,9,9a,10-octahydroacridine-3,9-dione derivatives; 4-silyloxy-1-benzothiopyrylium triflates and benzothiopyran-4-ones behave analogously.

Over the last few years there has been a considerable interest in reactions with 2-aminobuta-1,3-dienes,[1] since it was shown that they can be employed as dienes in intermolecular Diels–Alder reactions[2] to yield the corresponding cyclization products with high diastereo- and enantio-selectivity. In most examples reported so far, the 2-aminobuta-1,3-dienes have been used in hetero Diels–Alder reactions with C=S, C=O, C=N and N=N dienophiles[3] and in homo Diels–Alder reactions with nitroolefins as dienophiles.[3c,4] Here we report on the first examples of the highly diastereoselective annulation of 4-quinolones and benzothiopyran-4-ones with 2-aminobuta-1,3-dienes.

Recently we have found that nucleophiles like silyl enol ethers and organometallic reagents undergo regioselective 1,2-additions to the C=N$^+$-bond of 4-silyloxyquinolinium triflates **2** (X = NR)[5a] and the C=S$^+$-bond of 4-silyloxy-1-benzothiopyrylium triflates **2** (X = S) (Scheme 1).[5b] Furthermore it was demonstrated that these positively charged heteroaromatic systems can be annulated in a highly regio- and diastereoselective manner employing unsubstituted as well as 3-mono- and 3,4-disubstituted 2-silyloxybuta-1,3-dienes.[6]



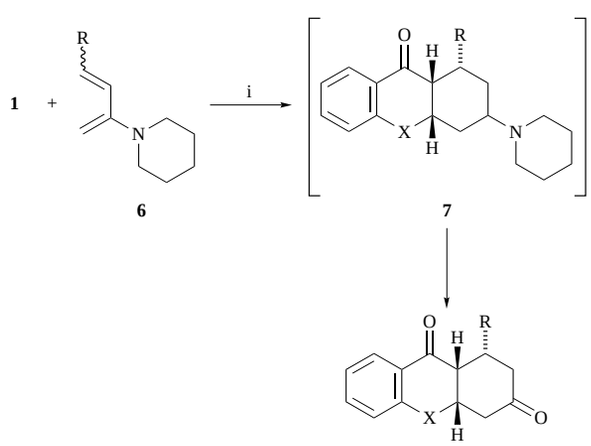
1,2,4,5 a: X = NCO_2Et **b**: X = NCbz **c**: X = S
3 a: NR_2 = morpholino **b**: NR_2 = piperidino **c**: NR_2 = pyrrolidino

Scheme 1 *Reagents and conditions:* i, **1** (1.0 equiv.), TIPSOTf (1.1 equiv.), room temp., 1 h; ii, CH_2Cl_2, **3** (2.0 equiv.), room temp., 30–60 min; iii, camphorsulfonic acid (1.0 equiv.), CH_2Cl_2, room temp., 2–3 h, 89% (**5a**); 76% (**5b**); 93% (**5c**)

To further explore the reactivity of 4-quinolones **1** (X = NR) and the corresponding 4-silyloxyquinolinium triflates **2** (X = NR), their reactions with enamines and 2-aminobuta-1,3-dienes were investigated. It was found that reaction of the *N*-protected 4-silyloxyquinolinium triflates **2a**,**b** with the enamines **3a–c** proceeds *via* 1,2-addition to the C=N$^+$ bond to give exclusively adducts **4a**,**b** in high yields (Scheme 1, Table 1).† The products were isolated as mixtures of their *syn*- and *anti*-diastereomers with ratios varying from 1.7:1.0 to 3.4:1.0, but so far the relative stereochemistry of the diastereomeric 1,2-addition products **4a**,**b** has not been established beyond any doubt. By performing the reaction of the benzothiopyrylium triflate **2c** with **3a**, which yields *syn*-**4c** and *anti*-**4c** in a 1.0:2.1 ratio (Scheme 1, Table 1), it was demonstrated that the 1,2-additions with enamines are not restricted to quinolinium salts.

It is remarkable, however, that in order to obtain high yields of the 1,2-adducts it is necessary (*a*) to run the reactions in the absence of any bases like 2,6-lutidine and (*b*) to avoid aqueous work up. The hydrolysis of the silyl enol ethers **4** could easily be achieved by using camphorsulfonic acid (CSA) (Scheme 1). In addition, the diastereomeric keto silyl enol ethers *syn*-**4a** and *anti*-**4a** were hydrolyzed separately and it was found that under these conditions no isomerization occurred at C-2′.

Surprisingly, no reaction was observed when the 4-silyloxyquinolinium triflates **2** and the 2-aminobuta-1,3-dienes **6** were reacted under the conditions that had been established for the 1,2-addition process (Scheme 2). After some experimentation it was discovered that the annulation could be achieved



1 a: X = NCO_2Et **b**: X = NCbz **c**: X = S
6 a: R = Pr^i **b**: R = Bu^t **c**: R = *c*-C_6H_{11}

7,8 a: R = Pr^i, X = NCO_2Et **b**: R = Bu^t, X = NCO_2Et
c: R = *c*-C_6H_{11}, X = NCO_2Et **d**: R = Pr^i, X = NCbz
f: R = *c*-C_6H_{11}, X = NCbz **g**: R = Pr^i, X = S

Scheme 2 *Reagents and conditions:* i, **1** (1.0 equiv.), CH_2Cl_2, BF_3·Et_2O (1.0 equiv.), then **6** (1.5 equiv.), room temp., 60 min

† Satisfactory analytical (combustion and/or high-resolution mass) and spectral (UV, IR, NMR and MS) data were obtained for all compounds.

Table 1 Formation of **4** by 1,2-addition of enamines **3** to positively charged aromatic heterocyclic systems **2**

Entry	**1, 2**	X	**3**	NR_2	**4**	Yield[a] **4** (%)
1	**a**	NCO_2Et	**a**	morpholino	**a**	81
2	**a**	NCO_2Et	**b**	piperidino	**a**	86
3	**a**	NCO_2Et	**c**	pyrrolidino	**a**	84
4	**b**	NCbz	**a**	morpholino	**b**	87
5	**c**	S	**a**	morpholino	**c**	93

[a] After column chromatography.

Table 2 Diastereoselective formation of annulation products **8** by reaction of **1** with 2-aminobuta-1,3-dienes **6**

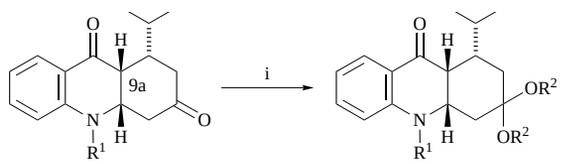
Entry	**1**	X	**6**	R	**8**	Yield[a] **8** (%)
1	**a**	NCO_2Et	**a**	Pr^i	**a**	74
2	**a**	NCO_2Et	**b**	Bu^t	**b**	31
3	**a**	NCO_2Et	**c**	*c*-C_6H_{11}	**c**	65
4	**b**	NCbz	**a**	Pr^i	**d**	54
5	**b**	NCbz	**b**	Bu^t	**e**	—
6	**b**	NCbz	**c**	*c*-C_6H_{11}	**f**	63
7	**c**	S	**a**	Pr^i	**g**	72

[a] After column chromatography.

when 4-quinolones **1**, instead of the 4-silyloxyquinolinium triflates **2** were reacted with the 2-aminobuta-1,3-dienes **6** and $BF_3{\cdot}Et_2O$ as a Lewis acid. Best results were obtained with 1.1 equiv. of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature. Under these conditions the reaction of the *N*-ethoxycarbonyl-protected 4-quinolone **1a** with the 4-isopropyl-substituted 2-aminobuta-1,3-diene **6a** yielded the *cis*,*cis*-1,2,3,4,4a,9,9a,10-octahydroacridine-3,9-dione **8a** with three stereogenic centers exclusively in 74% yield.‡ The reaction of **1a** with the 4-*tert*-butyl- and the 4-cyclohexyl-substituted 2-aminobuta-1,3-dienes **6b** and **6c** gave the corresponding annulation products **8b** and **8c** in diastereomeric pure form (Table 2, entries 1–3; Scheme 2). Similar results were obtained in the annulation of **6a** and **6c** with the *N*-benzyloxycarbonyl (Cbz)-protected 4-quinolone **1b** (Table 2, entries 4, 6; Scheme 2). No product, though, was formed in the reaction of **1b** with the 4-*tert*-butyl-substituted 2-aminobuta-1,3-diene **6b** (Table 2, entry 5; Scheme 2). It is interesting to note that the transformations cannot be performed with the *N*-methyl- and the unprotected 4-quinolones. This type of annulation process is not restricted to quinolones but can also be used for the synthesis of thioxanthene-3,9-dione derivatives as was demonstrated by the reaction of **1c** with **6a**. Here, the diastereomerically pure *cis*,*cis*-annulation product **8g** was isolated in 72% yield (Table 2, entry 7; Scheme 2).

The structural elucidation of the cyclization products was mainly based on NMR studies. For example, ^{1}H NMR- and 2D-COSY-experiments allowed an unambiguous configurational assignment of **8a**.§ In addition, an X-ray crystal structure analysis could be obtained for **8a**.¶ The transformations may either proceed as more or less concerted intermolecular Diels–Alder reactions with normal electron demand or as anionic Domino processes,[6,7] where in the first step an intermolecular 1,4-addition of the enamine to the vinylogous amide takes place. This is followed by an intramolecular 1,4-addition of the enolate to the conjugated iminium ion—both newly formed in the first addition step. Apart from the high diastereoselectivity of the process it is clearly an advantage that the hydrolysis of the enamines **7**, which are believed to occur as intermediates, needs no extra step but simply takes place under aqueous work-up conditions.‡ The 2-aminobuta-1,3-dienes **6** were prepared in accordance with the procedures published by Enders *et al.*[3a] and Barluenga *et al.*,[8] and the *N*-protected 4-quinolones **1a**,**b** were obtained by standard procedures.[9]

For further transformations it was necessary to know whether the two keto groups formed during the annulation process could easily by discriminated. For this purpose the acetalization of **8a** and **9** (**9** could be obtained by hydrogenolytic cleavage of the Cbz group in **8d**) (H_2 Pd/C, 80%) was investigated. It was found that acetalization of both **8a** and **9** proceeded exclusively at C-3 to yield **10a**,**b** (Scheme 3). These



8a: $R^1 = CO_2Et$ 78% **10a**: $R^1 = CO_2Et$, $R^2 = Et$
9: $R^1 = H$ 80% **10b**: $R^1 = H$, $R^2 = Me$

Scheme 3 *Reagents and conditions:* i, CSA (2.0–5.0 equiv.), R^2OH, room temp., 30–60 min

results demonstrate the different reactivity of the two keto functions. Under these reaction conditions no isomerization took place at C-9a. Further work is now directed to the synthesis of enantiomerically pure annulation products using 2-aminobuta-1,3-dienes of C_2-chiral amines.[10]

In summary we have established that substituted 2-amino-

‡ General procedure for the synthesis of **8**: boron trifluoride–diethyl ether (1.1 mmol) and a 2-aminobuta-1,3-diene **6** (1.5 mmol) were successively added to a stirred solution of **1** (1.0 mmol) in dry dichloromethane (15 cm^3) under argon at room temperature. The reaction mixture was stirred for 1 h at room temperature. After quenching the reaction by addition of saturated aq. sodium hydrogen carbonate (5 cm^3) and further stirring for 10 min at room temperature the aqueous phase was extracted twice with dichloromethane (2 × 5 cm^3). The combined organic layers were dried over sodium sulfate, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel with ethyl acetate–light petroleum (bp 40–60 °C) (1:4) as eluent to yield the annulation product **8**. In addition, starting material **1** and unidentified decomposition products could be isolated as side products. No diastereomeric annulation products **8** were found.

§ Selected data for **8a**: δ_H(300 MHz; C_6D_6; Me_4Si; *J* in Hz) 0.66 [d, $^3J_{CH_3,\ CH}$ 6.5, 6H, $CH(CH_3)_2$], 0.83 (ddt, $^3J_{1\text{-}H,\ CH}$ 10.0, $^3J_{1\text{-}H,\ 2\text{-}Hax}$ 14.0, $^3J_{1\text{-}H,\ 2\text{-}Heq}$ 3.5, $^3J_{1\text{-}H,\ 9a\text{-}H}$ 3.5, 1H, 1-H), 0.96 (t, $^3J_{CH_3,\ CH_2}$ 7.0, 3H, $CO_2CH_2CH_3$), 2.13 (dd, $^2J_{4\text{-}Hax,\ 4\text{-}Heq}$ 15.0, $^3J_{4\text{-}Hax,\ 4a\text{-}H}$ 13.0, 1H, 4-H_{ax}), 2.18 (dd, $^2J_{2\text{-}Hax,\ 2\text{-}Heq}$ 16.5, $^3J_{2\text{-}Hax,\ 1\text{-}H}$ 14.0, 1H, 2-H_{ax}), 2.36–2.49 (m, 2H, 2-H_{eq}, 4-H_{eq}), 2.57 (dseptet, $^3J_{CH,\ 1\text{-}H}$ 10.0, $^3J_{CH,\ CH_3}$ 6.5, 1H, 2′-H), 2.98 (m, 1H, 9a-H), 3.96–4.08 (m, 2H, $CO_2CH_2CH_3$), 4.90 (dt, $^3J_{4a\text{-}H,\ 4\text{-}Hax}$ 13.0, $^3J_{4a\text{-}H,\ 4\text{-}Heq}$ 5.0, $^3J_{4a\text{-}H,\ 9a\text{-}H}$ 5.0, 1H, 4a-H), 6.78 (dt, $^3J_{7\text{-}H,\ 6\text{-}H}$ 7.5, $^3J_{7\text{-}H,\ 8\text{-}H}$ 7.5, $^4J_{7\text{-}H,\ 5\text{-}H}$ 1.0, 1H, 7-H), 7.25 (ddd, $^3J_{6\text{-}H,\ 5\text{-}H}$ 7.5, $^3J_{6\text{-}H,\ 7\text{-}H}$ 8.5, $^4J_{6\text{-}H,\ 8\text{-}H}$ 2.0, 1H, 6-H), 8.11 (d, $^3J_{5\text{-}H,\ 6\text{-}H}$ 9.0, 1H, 5-H), 8.14 (dd, $^3J_{8\text{-}H,\ 7\text{-}H}$ 7.5, $^4J_{8\text{-}H,\ 6\text{-}H}$ 1.5, 1H, 8-H); δ_C(75 MHz; C_6D_6; Me_4Si) 14.31 ($CO_2CH_2CH_3$), 21.13 [$CH(CH_3)_2$], 21.66 [$CH(CH_3)_2$], 30.04 [$CH(CH_3)_2$], 41.80 (C-2), 41.88 (C-4), 44.91 (C-1), 47.30 (C-9a), 56.26 (C-4a), 62.72 ($CO_2CH_2CH_3$), 123.33 (C-5), 123.70 (C-7), 124.24 (C-8a), 127.39 (C-8), 134.64 (C-6), 140.65 (C-10a), 153.30 ($CO_2CH_2CH_3$), 193.51 (C-9), 204.99 (C-3).

¶ *Crystal structure solution and refinement:* diffraction data were collected on a Siemens–Stoe AED four-circle diffractometer at 183 K with Mo-Kα radiation (λ = 0.710 73 Å). The structure was solved by direct methods with SHELX-86 and refined by full-matrix least-squares on F^2 (SHELX-93). Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted in calculated positions. *Crystal data:* $C_{19}H_{23}NO_4$, M = 329.38, triclinic, space group P1, a = 932.3(10), b = 1189.7(10), c = 1668(2) pm, α = 107.42(10), β = 91.05(5), γ = 95.61(6)°, V = 1.754(3) nm^3, Z = 4, D_c = 1.247 Mg m^{-3}, μ_{calc} = 0.087 mm^{-1}, $F(000)$ = 704, crystal size 1.0 × 1.0 × 1.0 mm, 5533 collected reflections, 4022 independent reflection, goodness of fit 1.068, refinement converged for all data with R = 0.0542 and R_w = 0.1360. Atomic coordinates, bond lengths, bond angles and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/140. The single X-ray analysis of **8a** was performed by Dr M. Noltemeyer and H.-G. Schmidt (Institut für Anorganische Chemie, Tammannstr. 4, D-37077 Göttingen, Germany).

buta-1,3-dienes can be used for the highly diastereoselective annulation of 4-quinolones and benzothiopyran-4-ones. Furthermore it was demonstrated that enamines serve as nucleophiles for the regioselective 1,2-addition to 4-silyloxy-quinolinium triflates and 4-silyloxybenzothiopyrylium triflates.

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