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4-Methylpyrimidinium ylides. Part 7: 3+2 Dipolar cycloadditions to non-symmetrical substituted alkenes and alkynes

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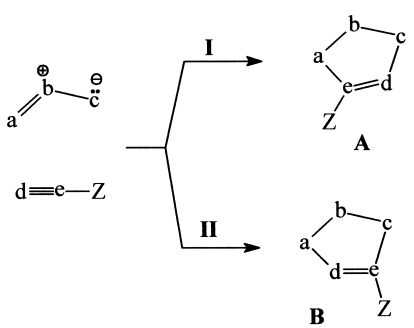
Abstract—The ability of 4-methylpyrimidinium ylides (as 1,3-dipoles) to react with activated non-symmetrical substituted dipolarophiles (alkenes and alkynes) is presented. 4-Methylpyrimidinium ylides did not react with alkenes. With alkynes the reactions are regiospecific, a single regioisomer being obtained. A possible mechanism for the reaction pathway is proposed. For the first time in the pyrimidinium ylides series both isomers resulting from bonding to the 2-and 6-positions of the heterocycle ring were obtained. The appropriate conditions in order to increase the selectivity of one of the isomers were determined.

1. Introduction

The [3+2] dipolar cycloaddition reactions of cycloimmonium ylides to non-symmetrical substituted dipolarophiles are rather old and well known reactions.[1–5] Despite this, these reactions are still widely discussed because of their theoretical and practical interest.[6–11] In these reactions, the addition of the dipole (ylide) to the dipolarophile in a double sense (regiochemistry) has often been found, in accordance with the orbital, steric and electronic factors (Scheme 1). Also, the reaction is a convenient way to obtain azabicyclic compounds, which are otherwise very difficult or even impossible to prepare. On the other hand, azabicyclic compounds show biological activity[12–14] [antimicrobial, antineoplastic, antiviral, anti-AIDS, antituberculosis, etc.] which substantially increases the value of these compounds. Therefore, we have studied the reaction of 4-methylpyrimidinium ylides with non-symmetrical substituted alkenes and alkynes.



Scheme 1.

2. Results and discussions

As we have shown in a previous work,[15] pyrimidinium ylides can be described by a 1,3-dipolar structure, having a 'sextet' without a double bond with internal octet stabilisation. The 1,3-dipolar activity could involve either the 2-or 6-position of the pyrimidine ring, supplementary regiochemical problems being involved. Until now, the literature data show that the cycloaddition takes place in either the 6 or the 2 position.[2,3,5,10,11]

In order to study the regiochemistry of the [3+2] dipolar cycloaddition reactions of 4-methylpyrimidinium ylides (generated in situ from the corresponding cycloimmonium salts[16]) with non-symmetrical substituted dipolarophiles, we chose as dipolarophiles acrylonitrile and ethyl acrylate (as alkenes) and methyl propiolate (as an alkyne) (Scheme 2).

The reaction with non-symmetrical substituted alkenes did not take place under the experimental conditions we employed. We got only dimers with a bispyrimidinopyrazine structure of type (**5**). A plausible explanation is the low reactivity of alkenes and the high reactivity of 4-methylpyrimidinium ylides which tend to react with one another via [3+3] dipolar cycloaddition, thus leading to dimers (the structure of such dimers was presented in a previous paper).[17]

The reaction with non-symmetrical substituted alkyne,

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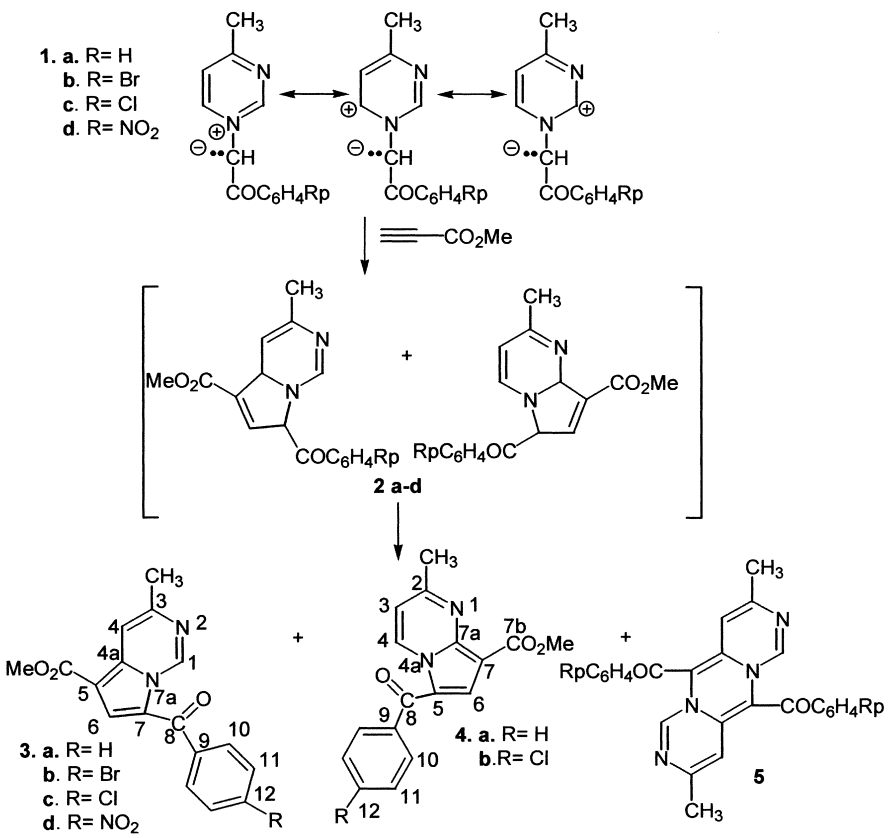

Scheme 2.

methyl propiolate, led to a mixture of pyrrolo[1,2-*c*]pyrimidine, (**3a**–**d**), (cycloadditions in 6), pyrrolo[1,2-*a*]pyrimidine, (**4a**,**c**), (cycloadditions in 2), as well as dimers, (**5**), of the corresponding ylides (the compounds were separated by flash chromatography). The reactions with propiolate occur as a normal [3+2] dipolar cycloaddition leading in first instance to the saturated cycloadducts (**2a**–**d**), which via an oxidative dehydrogenation lead to the more stable aromatised cycloadducts (Scheme 2).

The first task of this study was to highlight the reaction selectivity in order to increase the percentage of one of the desired compounds (**3**) or (**4**) and to decrease the ratio of undesired dimers (**5**) (Table 1). We performed the reaction under different conditions (temperatures, solvents, etc.). The best conditions were to run the reaction at room temperature and to add triethylamine extremely slowly, over 3–4 days. The selectivity of the reaction depends primarily on two factors: on the nature of substituent R at the *para* position of the benzoyl ring as well as on the reaction conditions. However, the substituent R seems to be decisive.

As for the regiochemical problems, we got isomers in both 2-and 6-positions of the heterocycle ring (for the first time in the pyrimidinium ylides series) for ylides **1a** and **1c** and only in the 6-position for **1b** and **1d**. A possible explanation for this behavior could be the higher stability of ylides **1b** and **1d** (due to the influence of the R-substituent from the *para* position of benzoyl ring[16]) which favours the canonical structures with the positive charge in the 6-position. The same explanation could be valid for selectivity.

Besides the regiochemical problems, one of the main tasks was to study the regioselectivity involved. As can be seen in Scheme 2, we find that in the case of 4-methylpyrimidinium ylides, the bond is formed between the ylide carbon and the non substituted carbon atom of the propiolate (path **I**, regioisomer **A**, Scheme 1). This is in accordance with the electronic effects exerted in the propiolate. A single regioisomer is obtained, which means that the reaction is regiospecific under a charge control.

The structures of regioisomers **A**, **3** and **4**, were proved by

Table 1. The results (%) of the selective study of the reaction between 4-methylpyrimidinium ylides and methyl propiolate

Ylide	Cycloadditions in 6		Cycloadditions in 2		Dimers (%)
	Cycloadduct	%	Cycloadduct	%	
1a, R=H	**3a**	15	**4a**	33	27
1b, R=Br	**3b**	32.5	–	–	32.5
1c, R=Cl	**3c**	31.5	**4c**	7	24.5
1d, R=NO_2	**3d**	41	–	–	49

elemental and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and MS). Obviously, the data furnished by the elemental analysis are compatible with both types of regioisomers. However, the data offered by the spectral analysis, confirm that **A** type products are obtained. Thus, analysis of the spectra, such as those of pyrrolo[1,2-*c*]pyrimidine, (**3a**), and pyrrolo-[1,2-*a*] pyrimidine, (**4a**), as representatives of series, reveals the following data.

In the ^{1}H NMR spectrum of pyrrolo[1,2-*c*]pyrimidine (**3a**) the most important signals are those of the H_1, H_4 and H_6 atoms. The H_1-atom appears at δ=10.52 ppm (singlet, 1H) which excludes cyclisation in the 2-position. This is also confirmed by the fact that the H_4-atom appears as a singlet (δ=8.03 ppm, 1H) while for a regioisomer in the 2-position it would have to appear as a doublet. The H_6-atom appears at δ=7.81 ppm (singlet, 1H), due to the deshielding effect induced by the methoxycarbonyl and benzoyl groups. The fact that this proton appears at a chemical shift approximately one ppm higher than that of a classical pyrrolo proton is a good proof for the **A** type (Scheme 1) regioisomer.

In the ^{1}H NMR spectrum of pyrrolo[1,2-*a*]pyrimidine (**4a**) the most important signals are those of the H_3, H_4 and H_6 atoms. Thus, the H_4-atom appears at δ=8.88 (1H_4, d, J=7.5 Hz) due to the coupling with H_3-atom (δ=6.13, 1H_3, d, J=7.5 Hz). These are good arguments for cyclisation in the 2-position. The H_6-atom appears at δ=7.96 ppm (singlet, 1H), the explanation given above (in the case of H_6 from **3a**) remaining valid.

The ^{13}C NMR spectrum also confirmed the proposed structures. Thus, in the case of compound (**3a**) the most important signals are those of the carbonyl carbons (C_8 and C_{5a}) and C_5, C_6 (pyrrolo β-endocyclic carbons). The C_8 carbon is the most deshielded (δ=185.34 ppm), characteristic for diaryl ketone. The C_{5a} carbon follows at 164.06 ppm (ester carbonyl). The C_5 and C_6 carbons offer very important proof for the **A** type regioisomeric structure. Thus, C_6 is much deshielded (117.76 ppm, β pyrrolo ring, β carboxy and benzoyl) compared with C_5 (105.21 ppm, β pyrrolo ring, α carboxy); also the relative intensity of the two carbons are in according with the proposed structure: carbon C_6, being tertiary, has a double intensity as compared with C_5 (quaternary carbon). In the case of compound (**4a**), analysis was done in the same manner: the C_8 carbon is the most deshielded (δ=186.18 ppm, diaryl ketone); C_{7b} (166.01 ppm, ester carbonyl); C_6 (tertiary carbon, 118.64 ppm, β pyrrolo ring, β carboxy and benzoyl) has a double intensity as compared with C_7 (quaternary carbon, 108.96 ppm, β pyrrolo ring, α carboxy).

The mass spectra also confirm the structure of the products. In the MS spectrum of compound (**3a**) the most important MS fragments are: 296 (BP, M^+); 298 (18%, M+2), 265 (56%, M^+-31 [CH_2=OH]); 237 (21%, M^+-59 [$COOCH_3$]); 219 (25%, M^+-77 [C_6H_5]); 105 (17%, C_6H_5CO); 77 (31%, C_6H_5). The main fragmentation reactions are fragmentation at the CO ester and ketone groups. The MS spectra of compound (**4a**) also confirm the structure but the fragmentation reactions are different: 296 (1%, M^+); 257 (BP, M^+-39 [C_3H_3]); 105 (34%, C_6H_5CO); 77 (30%, C_6H_5). The main fragmentation reactions are fragmentation of the aromatic ring and at the CO ketone group.

All the remaining signals in ^{1}H-, ^{13}C NMR and MS are in accordance with the proposed structure.

3. Conclusions

1. The reaction of 4-methylpyrimidinium ylides with activated non-symmetrical substituted alkynes occurs as a [3+2] dipolar cycloaddition leading to new azabicyclic compounds. 4-Methylpyrimidinium ylides did not react with alkenes.
2. A selective route to obtain the azabicyclic compounds derived from 4-methylpyrimidine via these reactions has been found.
3. Regioselectivity: a single regioisomer is obtained, which means that the reaction is regiospecific.
4. As for the regiochemical problems, we got both isomers in 2-and 6-position of the heterocycle ring for ylides (**1a**) and (**1c**) (for the first time in the pyrimidinium ylides series) and only in the 6-position for (**1b**) and **1d**. A possible explanation is presented.
5. Six new pyrrolopyridazine heterocycles have been obtained.

4. Experimental

^{1}H- and ^{13}C NMR spectra were run on a Bruker Avance at 400 MHz and were recorded in ppm downfield from an internal standard, $SiMe_4$ in $CDCl_3$. The coupling constants are given in Hz. The mass spectra were recorded on a VESTEC spectrometer by electron impact. The IR spectra were recorded with a SPECORD-71 spectrometer in KBr. The melting points are uncorrected. Technical grade nitrogen has been employed (98%).

4.1. General procedure

The cycloimmonium salt (10 mmol) and methyl propiolate (15 mmol) were dissolved in 10 mL of acetonitrile. Triethylamine (11 mmol, dissolved in 15 mL acetonitrile) was then added dropwise over 4 days (stirring, under nitrogen). The resulting mixture was precipitated with water, filtered at vacuum and washed thoroughly with water. The dried crude products were first recrystallized from methanol and then purified by flash chromatography (on silica using dichloromethane–acetone 98:2). Each product was then washed with an appropriate solvent.

4.1.1. 5-Methoxycarbonyl-3-methyl-7-benzoylpyrrolo-[1,2-*c*]pyrimidine, (3a). Washed with methyl *iso*-butyl ketone. Yellow cubic crystals, mp 134°C. Anal. $C_{17}H_{14}N_2O_3$: Calcd. C 69.3, H 4.76, N 9.52; Found C 69.2, H 4.70, N 9.47. IR (KBr, cm^{-1}): 1730 $\nu_{C=Oest.}$ (s); 1650 $\nu_{C=Oket.}$ (s); 1595, 1515, 1470, 1405 $\nu_{C=C,C=N}$ (s–m); 1220, 1110 ν_{C-O-C} (s); 2950 $\nu_{C-Haliph.}$ (w). ^{1}H NMR ($CDCl_3$, δ, ppm): 10.52 (1H_1, s), 8.03 (1H_4, s), 7.81 (1H_6, s), 7.83 (2H_{10}, d, J=8 Hz), 7.52 (2H_{11}, t, J=8, 7 Hz), 7.60

($1H_{12}$, t, J=7 Hz), 3.90 (3H, $COOCH_3$, s), 2.63 (3H, CH_3, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 185.34 (C═O), 164.06 (COO), 152.32 (C_1), 140.71 (C_3+C_9), 139.08 (C_{4a}), 132.02 (C_{12}), 129.93 (C_4), 129.01 (C_{10}), 128.58 (C_{11}), 122.12 (C_7), 117.76 (C_6), 105.22 (C_5), 51.46 (OCH_3), 23.89 (CH_3). MS—see text.

4.1.2. 5-Methoxycarbonyl-3-methyl-7-(*p*-bromobenzoyl)-pyrrolo[1,2-*c*]pyrimidine, (3b). Washed with methanol. Yellow cubic crystals, mp 205°C. Anal. $C_{17}H_{13}N_2O_3Br$: Calcd. N 7.50; Found N 7.45. IR (KBr, cm^{-1}): 1730 $\nu_{C=Oest.}$ (s); 1645 $\nu_{C=Oket.}$ (s); 1615, 1515, 1405 $\nu_{C=C,C=N}$ (s−m); 1220, 1110 ν_{C-O-C} (s); 2950 $\nu_{C-Haliph.}$ (w). ^1H NMR ($CDCl_3$, δ, ppm): 10.48 ($1H_1$, s); 8.03 ($1H_4$, s), 7.72 ($1H_6$, s), 7.74 ($2H_{10}$, d, J=8 Hz), 7.67 ($2H_{11}$, d, J=8 Hz), 3.91 (3H, $COOCH_3$, s), 2.63 (3H, CH_3, s).

4.1.3. 5-Methoxycarbonyl-3-methyl-7-(*p*-chlorobenzoyl)-pyrrolo[1,2-*c*]pyrimidine, (3c). Washed with acetone. Yellow cubic crystals, mp 195°C. Anal. $C_{17}H_{13}N_2O_3Cl$: Calcd. N 8.52; Found N 8.50. IR (KBr, cm^{-1}): 1730 $\nu_{C=Oest.}$ (s); 1645 $\nu_{C=Oket.}$ (s); 1590, 1515, 1470, 1450, 1405 $\nu_{C=C,C=N}$ (s−m); 1220, 1110 ν_{C-O-C} (s); 2950 $\nu_{C-Haliph.}$ (w). ^1H NMR ($CDCl_3$, δ, ppm): 10.48 ($1H_1$, s); 8.04 ($1H_4$, s), 7.78 ($1H_6$, s), 7.78 ($2H_{10}$, d, J=8 Hz), 7.50 ($2H_{11}$, d, J=8 Hz), 3.91 (3H, $COOCH_3$, s), 2.63 (3H, CH_3, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 183.86 (C═O), 163.92 (COO), 152.59 (C_1), 148.88 (C_3), 140.62 (C_{12}), 138.46 (C_{4a}), 137.35 (C_9), 130.37 (C_{10}), 129.76 (C_4), 128.93 (C_{11}), 121.78 (C_7), 117.80 (C_6), 105.40 (C_5), 51.51 (OCH_3), 23.91 (CH_3).

4.1.4. 5-Methoxycarbonyl-3-methyl-7-(*p*-nitrobenzoyl)-pyrrolo[1,2-*c*]pyrimidine, (3d). Washed with methanol. Yellow-brick crystals, mp 201–204°C. Anal. $C_{17}H_{13}N_3O_5$: Calcd. N 12.38; Found N 12.05. IR (KBr, cm^{-1}): 1730 $\nu_{C=Oest.}$ (s); 1645 $\nu_{C=Oket.}$ (s); 1525, 1350 ν_{NO_2} (s);1600, 1470, 1400 $\nu_{C=C,C=N}$ (s−m); 1220, 1110 ν_{C-O-C} (s); 2950 $\nu_{C-Haliph.}$ (w). ^1H NMR ($CDCl_3$, δ, ppm): 10.50 ($1H_1$, s); 8.05 ($1H_4$, s), 7.80 ($1H_6$, s), 7.68 ($2H_{10}$, d, J=8 Hz), 7.78 ($2H_{11}$, d, J=8 Hz), 3.90 (3H, $COOCH_3$, s), 2.63 (3H, CH_3, s).

4.1.5. 7-Methoxycarbonyl-2-methyl-5-benzoylpyrrolo-[1,2-*a*] pyrimidine, (4a). Washed with methanol. White-yellow needle crystals, mp 138°C. Anal. $C_{17}H_{14}N_2O_3$: Calcd. C 69.3, H 4.76, N 9.52; Found C 69.2, H 4.70, N 9.50. IR (KBr, cm^{-1}): 1730 $\nu_{C=Oest.}$ (s); 1650 $\nu_{C=Oket.}$ (s); 1595, 1515, 1470, 1405 $\nu_{C=C,C=N}$ (s−m); 1220, 1110 ν_{C-O-C} (s); 2950 $\nu_{C-Haliph.}$ (w). ^1H NMR ($CDCl_3$, δ, ppm): 8.88 ($1H_4$, d, J=7.5 Hz), 6.13 ($1H_3$, d, J=7.5 Hz), 7.96 ($1H_6$, s), 7.84 ($2H_{10}$, d, J=8 Hz), 7.50 ($2H_{11}$, t, J=8 Hz, J=7 Hz), 7.60 ($1H_{12}$, d, J=7 Hz), 3.85 (3H, $COOCH_3$, s), 3.81 (3H, CH_3, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 186.18 (C═O), 166.01 (COO), 163.36 (C_{7a}), 139.92 (C_9), 138.13 (C_2), 132.83 (C_{12}), 131.57 (C_5), 129.44 (C_{10}), 128.53 (C_{11}), 128.32 (C_4), 124.26 (C_3), 118.64 (C_6), 108.96 (C_7), 51.97 (OCH_3), 29.76 (CH_3). MS-see text.

4.1.6. 7-Methoxycarbonyl-2-methyl-5-(*p*-chlorobenzoyl)-pyrrolo[1,2-*a*] pyrimidine, (4b). Washed with methanol. White-yellow needle crystals, mp 187°C. Anal. $C_{17}H_{13}N_2O_3Cl$: Calcd. N 8.52; Found N 8.50. IR (KBr, cm^{-1}): 1730 $\nu_{C=Oest.}$ (s); 1645 $\nu_{C=Oket.}$ (s); 1590, 1515, 1470, 1450, 1405 $\nu_{C=C,C=N}$ (s−m); 1220, 1110 ν_{C-O-C} (s); 2950 $\nu_{C-Haliph.}$ (w). ^1H NMR ($CDCl_3$, δ, ppm): 7.70 ($1H_4$, d, J=7.5 Hz), 5.82 ($1H_3$, d, J=7.5 Hz), 8.24 ($1H_6$, s), 7.78 ($2H_{10}$, d, J=8 Hz), 7.47 ($2H_{11}$, d, J=8 Hz), 3.84 (3H, $COOCH_3$, s), 3.73 (3H, CH_3, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 194.12 (C═O), 166.41 (COO), 164.21 (C_{7a}), 142.31 (C_2), 138.17 (C_{12}), 137.82 (C_5), 135.01 (C_4), 134.27 (C_3), 130.68 (C_{10}), 128.83 (C_{11}), 128.69 (C_6), 111.04 (C_7), 51.86 (OCH_3), 29.75 (CH_3).

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