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A new method for the synthesis of azaheterocycles based on cascade reactions of nitrogen- and phosphorus-containing ylides with methyl diazoacetate

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Abstract—A new approach to functionally substituted pyrazoles and pyridazines based on the interaction of diazoesters with triphenylphosphonium or pyridinium carbonyl ylides and subsequent reactions of the so formed reactive azines with a further equivalent(s) of the initial ylides followed by a cyclocondensation into the corresponding five- or six-membered heterocycles is described.

Earlier we have shown[1,2] that α-diazocarbonyl compounds are able to react with nitrogen- and phosphorus-containing ylides forming a covalent bond between the ylide carbon atom and the terminal nitrogen. However, the reaction did not stop at this point and proceeded to give esters of 3,4(4,5)-diazadienetri- or tetracarbonic acids as well as tetrahydropyridazine derivatives as a result of subsequent transformations. In some cases, polyfunctional phosphorus ylides were isolated.[2] These ylides, depending on the character of the substituents on the initial ylides and diazocompounds could be of interest for the synthesis of azaheterocycles containing a variety of functional groups.

In the present work, we report a new approach for the synthesis of polyfunctional pyrazoles and pyridazines, based on a series of cascade transformations of diazoesters and α-carbonyl-containing nitrogen and phosphorus ylides. The formation of functionally substituted azaheterocycles, which are difficult to prepare by other methods, in particular, by the 'hydrazine' procedure, occurs from readily available starting compounds.

We established that ylide **1**, obtained by the reaction of methyl (triphenylphosphoranylidene)acetate (**2**) with methyl diazoacetate[2] in the presence of a base, for example, triethylamine, at reflux in chloroform, underwent intra-molecular cyclization into N-substituted 5-methoxy-3-methoxycarbonylpyrazole **3** in 75% yield. ^{1}H and ^{13}C NMR spectra of the crude product showed that only one isomer had formed in this reaction.[3] The formation of pyrazole **3** appeared to occur as a consequence of isomerization of ylide **1** under the action of Et_3N into zwitterion **4**, which underwent cyclization to betaine **5** which then eliminated triphenylphosphine oxide to give **3** (Scheme 1). This transformation involving a zwitterionic mechanism has analogy with the formation of 5-methoxy-1-phenylpyrazoles via reaction of phosphorane **2** with substituted aminonitriles.[4]

It turned out that the synthesis of pyrazole **3** could be carried out without preliminary preparation of ylide **1**. Thus, if an equivalent amount of triethylamine was added to a mixture of phosphoranylideneacetate **2** and methyl diazoacetate in chloroform and then refluxed for 12 h, the main reaction product isolated in ~65% yield was methoxypyrazole **3**.[3] A considerable reduction of the reaction time (by several fold) occurred for the synthesis of methoxypyrazole **3**, and intermediate ylide **1**, respectively, compared with the analogous experiment when triethylamine was absent. Triethylamine seems to participate both in the isomerization of ylide **1** to intermediate **4** and also in other early key stages leading to reactive diazadienes.

Pyrazole **3** bearing two different ester groups was selectively reduced with $NaBH_4$ in methanol (20 °C, 3 h) to form crystalline *N*-(2-hydroxyethyl)pyrazole **6** (see Scheme 2). The reduction proceeded at the aliphatic ester group, as confirmed by ^{1}H and ^{13}C NMR spectroscopies.[5]

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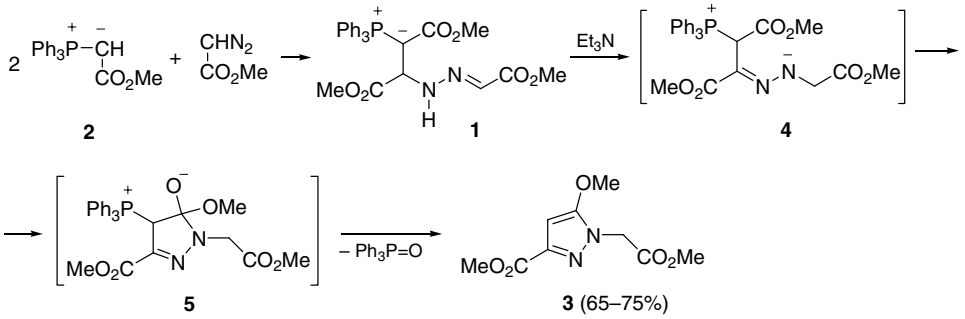
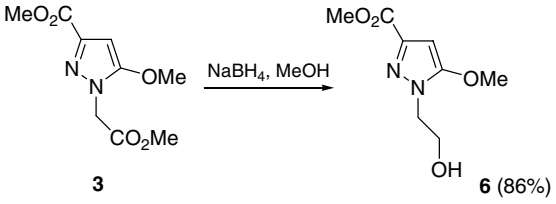


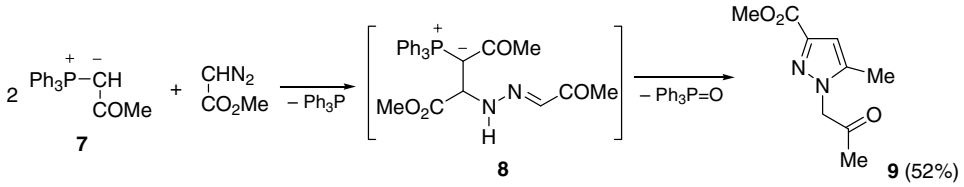
Scheme 1.



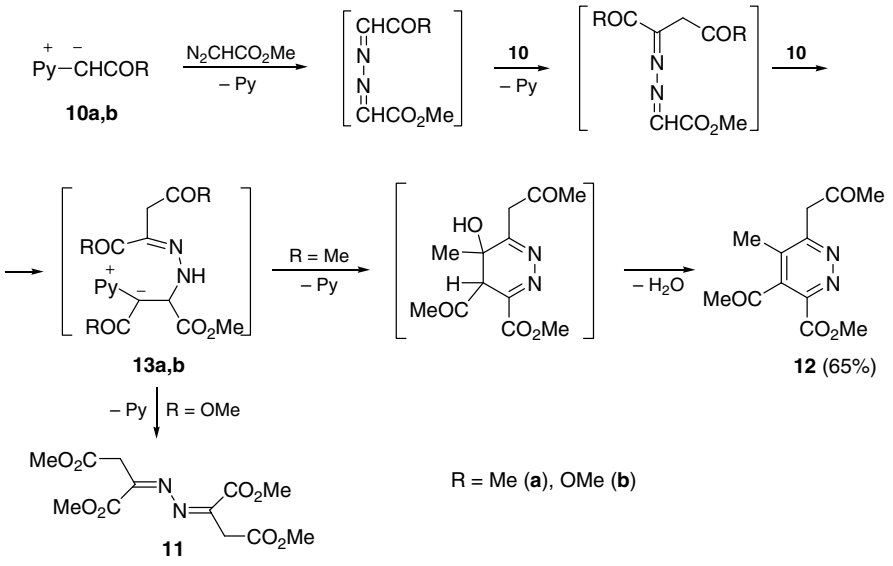
Scheme 2.

The reaction of methyl diazoacetate with 1-triphenylphosphoranylidenepropan-2-one (**7**) bearing a ketone group instead of an ester proceeded analogously to ylide **2**. However, in this case, ylide **8** was not detected in the reaction mixture and pyrazole **9** was obtained even without the addition of triethylamine.[6] Reaction of the second equivalent of ylide **7** with the intermediate highly reactive azine, in principle, could proceed on either of the two different electron-deficient C atoms of the two imine fragments, but in practice ylide attack is likely to occur on the C atom bearing the ester group (Scheme 3). The isolated pyrazole **9** has a 2-oxopropyl substituent, rather than a CH_2CO_2Me fragment. Reduction of pyrazole **9** with $NaBH_4$ gave the corresponding secondary alcohol.

Recently, we demonstrated that the reaction of diazoesters with pyridinium alkoxycarbonyl ylide (**10a**) proceeded through a series of successive reactions where each addition of ylide was accompanied by elimination of pyridine.[2] Owing to the greater reactivity of pyridinium ylides compared to analogous phosphorus ylides **1** and **2**, successive addition reactions of the ylide fragment resulted in products containing three ylide



Scheme 3.



Scheme 4.

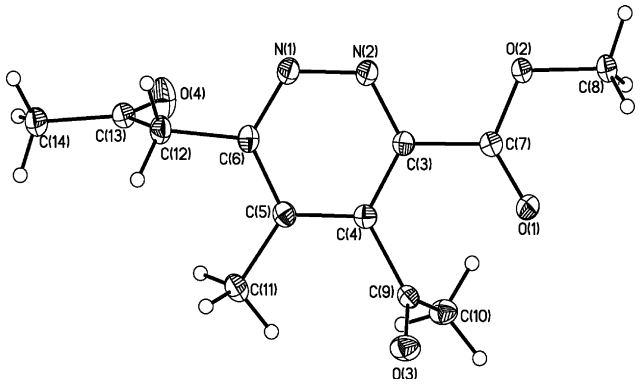


Figure 1. X-ray crystal structure of compound **12**.

fragments in one molecule of diazoester. In fact, the process stops on formation of substituted diazaalkadienes **11** with fully substituted C=N bonds.

It is interesting to note that contrary to methoxycarbonyl ylides, the reaction of methyl diazoacetate with pyridiniumcarbonyl ylide **10b** gave the unexpected functionally substituted pyridazine **12** instead of a carbonyl-containing diazaalkadiene. Pyridazine **12** probably results from differences during the last stage of the process, namely, transformations of pyridinium ylides **13a** and **13b**. The presence of the ester group in intermediate **13a** results in mainly the elimination of pyridine leading to diazaalkadiene **11**. However, the presence of carbonyl groups in intermediate **13b** resulted in intramolecular condensation providing the six-membered heterocycle (Scheme 4). As a result of this process, functionally substituted pyridazine **12** was obtained in 65% yield.[7]

The structure of pyridazine **12** was established from X-ray analysis[8] of crystals isolated from $CHCl_3$ solution by gradual addition of hexane (Fig. 1). According to the results obtained, compound **12** exists in the ketone form in the solid state. In solution (in accordance with the ^1H and ^{13}C NMR spectra), the enol form is present in a considerable amount. The ratio of tautomers depends on both the temperature and polarity of the solvent. The ratio of ketone to enol in dimethylsulfoxide is ~13:1, whereas in chloroform this ratio is 1:1.6.

The reactions of other carbonyl methylides with alkyl diazoacetates or diazoketones could also be accomplished.

In summary, we have developed a new, concise and efficient protocol to synthesize polyfunctional substituted pyrazoles and pyridazines based on cascade transformations of simple and available starting compounds. The obtained heterocycles could be of interest as close analogues of compounds demonstrating antiinflammatory, hypnotic[9] and analgesic activities.[10,11]

Acknowledgements

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2. Tomilov, Yu. V.; Platonov, D. N.; Dorokhov, D. V.; Kostyuchenko, I. V. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 112–117.
3. *Methyl 5-methoxy-1-(methoxycarbonylmethyl)pyrazole-3-carboxylate* (**3**). A solution of methyl (triphenylphosphoranylidene)acetate (1.54 g, 4.6 mmol), methyl diazoacetate (0.24 g, 2.4 mmol) and triethylamine (0.46 g, 4.6 mmol) in 10 mL of chloroform was refluxed for 12 h under an inert atmosphere. After cooling, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using benzene/ethyl acetate (1/1) as the eluent to afford compound **3**: 0.34 g (65%), pale-yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68, 3.84 and 3.86 (all s, $3\times3H$, $3OCH_3$), 4.76 (s, 2H, NCH_2), 6.05 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.7 (CH_2), 52.1, 52.7 and 59.2 ($3CH_3$), 86.9 (C(4)), 142.3 (C(3)), 156.1 (C(5)), 162.6 and 167.5 (2COO); EI-MS (*m*/*z*, relative intensity): 228 (M^+, 50), 197 [$(M-IMe)^+$, 34], 169 [$(M-CO_2Me)^+$, 100]. Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.16; H, 5.33; N, 12.09.
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5. *Methyl 5-methoxy-1-(2-hydroxyethyl)pyrazole-3-carboxylate* (**6**). Sodium borohydride (0.69 g, 18 mmol) was added in small portions over a period of 1 h to a stirred solution of pyrazole **3** (1.48 g, 6.5 mmol) in 10 mL of methanol and the mixture was then stirred for an additional 2 h. Most of the methanol was removed in vacuo and the residue was quenched with a small quantity of water and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried with Na_2SO_4 and after removing the solvent, 1-(2-hydroxyethyl)pyrazole **6** was obtained as colourless crystals: 86%; mp 137–138 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (br s, 1H, IH), 3.87 and 3.90 (both s, $2\times3H$, $2ICH_3$), 3.95 (br q, $J=5.6$ Hz, 2H, CH_2I), 4.16 (t, $J=5.5$ Hz, 2H, CH_2N), 6.09 (s, 1H, H(4)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.4 (CH_2N), 51.9 and 58.9 ($2OCH_3$), 60.7 (CH_2I), 86.8 (C(4)), 141.3 (C(3)), 155.8 (C(5)), 162.6 (COO); EI-MS (*m*/*z*, relative intensity): 200 (M^+, 32), 169 [$(M-IMe)^+$, 100], 156 [$(M-CH_2CH_2O)^+$, 54], 125 (48). Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 47.84; H, 5.88; N, 13.87.
6. *Methyl 5-methyl-1-(2-oxopropyl)pyrazole-3-carboxylate* (**9**). A solution of (triphenylphosphoranylidene)propan-2-one (0.76 g, 2.4 mmol) and methyl diazoacetate (0.24 g, 2.4 mmol) in 20 mL of dry acetonitrile was refluxed with stirring for 24 h. After cooling, the solvent was removed in vacuo and the mixture was purified by column chromatography on silica gel (benzene–EtOAc, 1:1) to afford compound **9**: 52%; yellowish oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H, CH_3), and 2.20 (s, 3H, CH_3CO), 3.88 (s, 3H, OCH_3), 4.91 (s, 2H, CH_2N), 6.61 (s, 1H, H(4)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0 (CH_3), 26.9 (CH_3CO), 52.1 (OCH_3), 59.2 (CH_2N), 108.7 (C(4)), 140.9 (C(5)), 143.0 (C(3)), 162.8 (COO), 200.2 (CO); EI-MS

(*m*/*z*, relative intensity): 196 (M^+, 28), 165 [$(M-IMe)^+$, 23], 154 (63), 153 (100), 122 (20). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.89; H, 6.28; N, 14.08.

7. *Methyl 4-acetyl-5-methyl-6-(2-oxopropyl)pyridazine-3-carboxylate* (**12**). A solution of *N*-(2-oxopropyl)pyridinium bromide (3.00 g, 20 mmol) and methyl diazoacetate (0.50 g, 5 mmol) in 40 mL of acetonitrile was stirred in the presence of potassium carbonate (7.60 g, 50 mmol) at room temperature for 16 h. Then, 150 mL of water was added, the mixture was extracted with methylene chloride (3×50 mL) and the combined organic layer was dried with Na_2SO_4. After removing the solvent, the residue was purified by column chromatography on silica gel (benzene–EtOAc, 1:1) to afford compound **12**: 65%; yellow crystals, mp 125–127 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ *keto-form* (93%): 2.13 and 2.52 (both s, 2×3H, $2ClCH_3$), 2.30 (s, 3H, CH_3 at C(5)), 3.95 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2); *enol-form* (7%): 2.01 (s, 3H, CH_3 at C(5)), 2.46 and 3.28 (both s, 2×3H, $2ClCH_3$), 3.87 (s, 3H, OCH_3), 5.58 (s, 1H, =CH), 15.4 (br s, 1H, OH). ^{1}H NMR (200 MHz, $CDCl_3$) δ *keto-form* (38%): 2.18 and 2.52 (both s, 2×3H, $2ClCH_3$), 2.30 (s, 3H, CH_3 at C(5)), 3.98 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2); *enol-form* (62%): 1.99 and 2.18 (both s, 2×3H, 2 CH_3), 2.50 (s, 3H, $ClCH_3$), 3.93 (s, 3H, OCH_3), 5.30 (s, 1H, =CH), 12.5 (br s, 1H, OH). ^{13}C NMR (50 MHz, DMSO-d_6) δ *keto-form*: 13.8 (CH_3 at C(5)), 29.4 and 30.6 ($2ClCH_3$), 47.8 (CH_2), 52.6 (ICH_3), 133.0, 140.2 (C(3), C(4)), 144.4 (C(5)), 160.6, 163.8 (CII and C(6)), 200.6 and 203.6 (2CI); *enol-form*: 13.4 and 26.0 (2 CH_3), 30.6 ($ClCH_3$), 52.3 (ICH_3), 88.6 (=CH), 130.6, 133.0 (C(3), C(5)), 140.2 (C(4)), 154.1, 159.0 (CII and C(6)), 186.1 (=C(OH)), 200.0 (CI). ^{13}C NMR (50 MHz, $CDCl_3$) δ *keto-form*: 14.6 (CH_3 at C(5)), 29.6 and 30.1 ($2ClCH_3$), 49.0 (CH_2), 53.4 (ICH_3), 136.9, 141.7, 145.3 (C(3), C(4), C(5)), 163.3, 164.5 (CII and C(6)), 200.6 and 202.7 (2CI); *enol-form*: 14.1 and 27.5 ($2CH_3$), 31.4 ($ClCH_3$), 53.2 (ICH_3), 89.0 (=CH), 131.0, 133.3, 139.2 (C(3), C(4), C(5)), 153.8, 160.2 (CII and C(6)), 189.7 (=C(OH)), 200.4 (CI). EI-MS (*m*/*z*, relative intensity): 250 (M^+, 20), 208 (20), 43 (100). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.21; H, 5.48; N, 10.88.
8. Crystallographic data for compound **12** have been deposited with the Cambridge Crystallographic Data Center with the registration number CCDC 610164. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk].
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