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Reaction of functionalized azomethine ylides with acetylenic dipolarophiles: the facile synthesis of functionalized 2*H*- and 1*H*-pyrroles

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Abstract—The reaction of functionalized azomethine ylides as C-unsubstituted nitrile ylide equivalents with acetylenic dipolarophiles is mentioned. Therein, the initially formed cycloadducts, 2,5-dihydropyrroles, by the reaction of the azomethine ylides with substituted acetylenes, undergo a fission reaction to afford 2*H*-pyrroles and the parent heterocyclic system. Some 2*H*-pyrroles isomerized to 1*H*-pyrroles under both thermal and acidic conditions.

The cycloaddition reaction of N-unsubstituted (NH) azomethine ylides with olefinic dipolarophiles has been a very attractive approach to the N-unsubstituted (NH) pyrrolidines, which are found widely in biologically and pharmacologically active compounds.[1] Typical methods for the generation of NH-azomethine ylides constitute of group rearrangement of α-metalloamides[2] and 1,2-prototropic[3] and N-metalation[4] routes of the imines of α-amino esters. The former two routes are uncatalyzed thermal processes, however those have not always accomplished the stereoselective cycloaddition of the resulting NH-azomethine ylides because of the harsh generation conditions. In a recent paper,[5] we reported that the NH-azomethine ylide **A**, which was generated by the 1,2-prototropic isomerization of the corresponding imine under extremely mild conditions underwent a cycloaddition reaction with *N*-phenylmaleimide (NPMI) to give a cycloadduct, proline derivative **B**, stereoselectively. More interestingly, the treatment of the cycloadduct **B** with acetic acid caused a fission reaction to afford dehydroproline derivative **C** and the parent heterocyclic system **D** in good yields, the former of which corresponds to the cycloadduct of C-unsubstituted nitrile ylide with NPMI. We, therefore, thought that we could propose an equivalent process to C-unsubstituted nitrile ylide cycloaddition reaction (Scheme 1).

Our next concern was directed toward the reaction of the functionalized NH-azomethine ylides with acetylenic dipolarophiles, because only few approaches to the general and effective preparation of 2*H*-pyrroles[6] had been reported compared with 1*H*-pyrroles. When the solution of aldehyde **1** with (DL)-phenylalanine methyl ester **2a** (1.5 equiv) in toluene was heated at 85 °C for 1 h and cooled to room temperature, dimethyl acetylenedicarboxylate (DMAD) was added to the reaction mixture and the mixture was allowed to stir at room temperature for 14 h. After the purification with silica gel column chromatography, the desired 2,5-dihydropyrrole **4a** (53%), Michael type adducts **5a** (44% as an *E*/*Z* mixture), 4-hydroxy-1*H*-pyrrole **6** (11%) and parent heterocycle **7** (9%) were obtained. Undesired products **5a** and **6** were formed from only the reaction of DMAD with amino ester **2a**.[7] The reaction of **1**, **2a**, and dibenzoylacetylene (DBZA) afforded the almost same results: 2,5-dihydropyrrole **8a** (36%), **9a** (47%; as an *E*/*Z* mixture), and **7** (6%) were formed. Single crystal X-ray structure analysis[8] for **4a** and **8a** showed that these were the cycloadducts of DMAD and DBZA to the (*E*,*E*)-azomethine ylide (*E*,*E*)-**3a**, respectively. Although the

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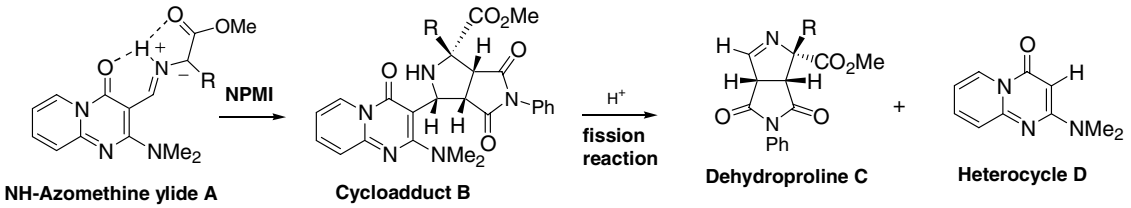
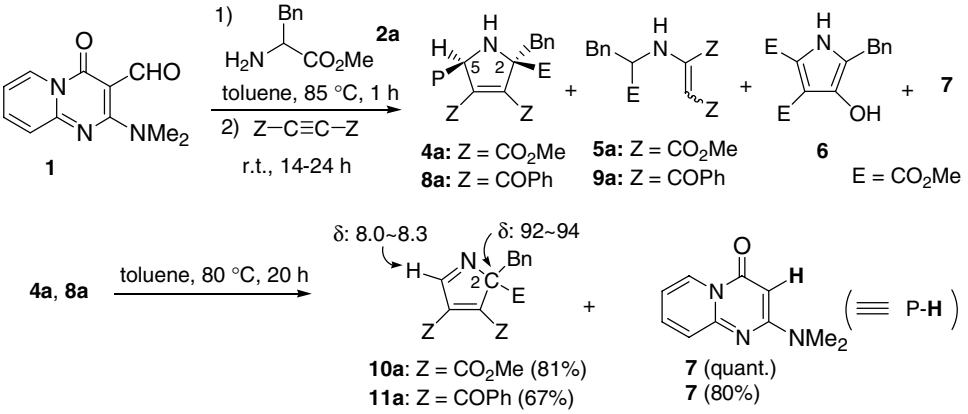
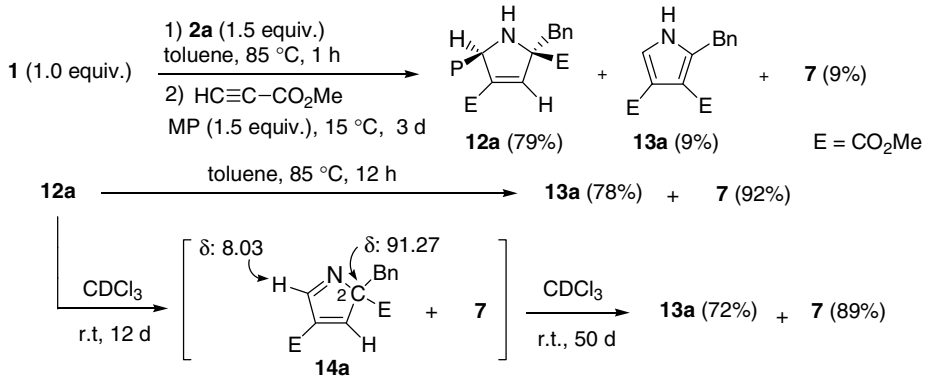


Scheme 1. Functionalized azomethine ylide **A** as C-unsubstituted nitrile ylide equivalent.

reaction conditions including solvent, temperature, reagent molar ratio, addition sequences and dehydrating reagent were examined, the yield of the cycloadducts **4a** and **8a** could not be improved. Gentle heating of **4a** and **8a** in toluene gave the desired 2*H*-pyrroles **10a**[9] and **11a** in moderate to good yields together with **7**. These mean that the reaction sequences are a novel and facile synthetic method for functionalized 2*H*-pyrroles in mild conditions (Scheme 2). Probably DMAD and DBZA are too reactive toward the amine nucleophile **2a** leading to **5a** and **9a** to accomplish efficiently the imine formation between aldehydes **1** and **2**. So, we chose methyl propiolate (MP) as the next acetylenic dipolarophile with less reactivity. The solution of **1** and **2a** in toluene was heated at 85 °C for 1 h, cooled down to room temperature, and MP was added to the solution. The reaction mixture was stirred at 15 °C for 3 d. The reaction underwent smoothly and regioselectively to give cycloadduct **12a** (79%), 1*H*-pyrrole **13a** (9%) and the parent heterocycle **7** (9%) with a depression of the formation of Michael type adduct such as **5a** and **9a**. The structure of cycloadduct **12a** was also confirmed by its single crystal X-ray analysis,[8] while that of 1*H*-pyrrole **13a** was determined by the comparison of the spectroscopic data reported in the literature.[10] Heating the isolated **12a** in toluene at 85 °C for 12 h gave 1*H*-pyrrole **13a** (78%) together with **7** (92%) and a small amount of unidentified product. Standing the chloroform-*d* solution of **12a** at room temperature for 12 days gave a mixture of 2*H*-pyrrole **14a**[11] and **7**. The 2*H*-pyrrole **14a** was not so stable and converted gradually to 1*H*-pyrrole **13a** together with a small amount of an unidentified product on further standing (for 50 days) at the same temperature (Scheme 3).



Scheme 2. The reaction of functionalized azomethine ylide **3a** with DMAD and DBZA and thermal behavior of cycloadducts **4a** and **8a**.



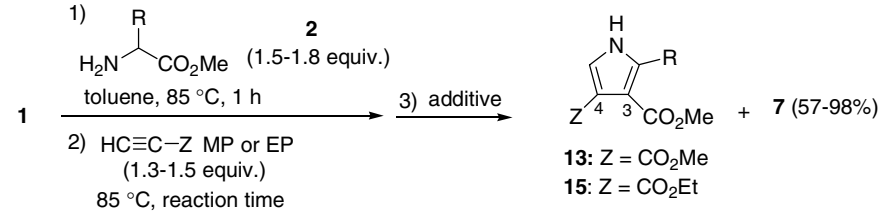
Scheme 3. The reaction of functionalized azomethine ylide **3a** with MP.

So, we applied the one-pot procedure to this reaction; the reaction of **1**, **2a**, and MP in toluene gave **13a** and **7** in 71% and 86% yield, respectively (Table 1; entry 1).[12] Stimulated by these findings, the similar reaction of **1**, amino esters **2b–f** and MP was examined. Although pyridinium *p*-toluene sulfonate (PPTS) was required for completing the reaction in many cases, the desired 1*H*-pyrroles **13b–f** and **7** were formed in moderate to good yields. These results are summarized in Table 1.

In order to obtain further information on the reaction path from **12** to **13**, the similar one-pot reaction of **1**, ethyl propiolate (EP) and **2a**, **2b**, and **2e** was also examined to give 1*H*-pyrrole **15a**, **15b**, and **15e** in good to excellent yields as single isomers together with **7** (Table 1; entries 12–14). Fortunately, recrystallization of **15a** from benzene afforded good single crystals for the X-ray structure analysis[8] and the structure of **15a** was confirmed to be 4-ethyl 3-methyl 2-benzylpyrrole-3,4-dicarboxylate. Although details are still unclear, a plausible pathway from **12** to **13** is demonstrated in Scheme 4; the elimination of the parent heterocycle **7** from cycloadduct **12** takes place thermally to afford 2*H*-pyrroles **14**, which undergo a 1,5-ester group rearrangement accompanied with the aromatization to 1*H*-pyrrole **13**.[15]

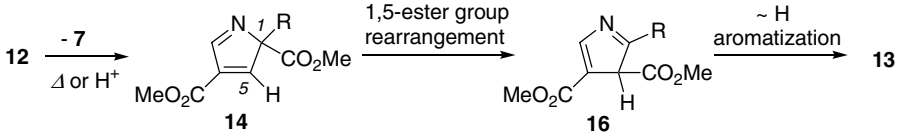
Our final concern in this one-pot reaction was focused on the generality of acetylenic dipolarophiles; the reac-

Table 1. The reaction of functionalized azomethine ylides **3** with MP and EP in a one-pot method

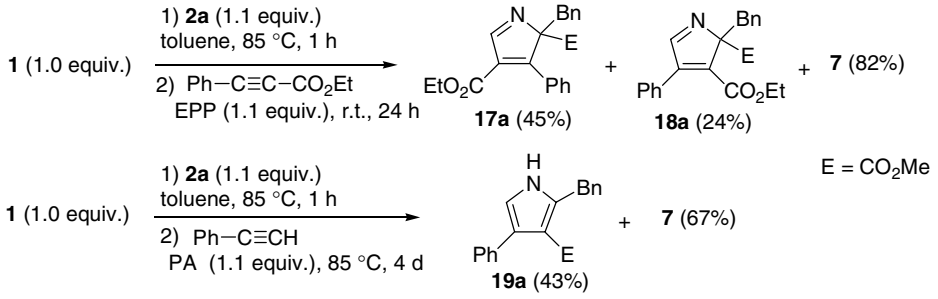


Entry	Amino ester/R	Propiolate/Z	Additive (equiv)	Reaction time (h)	1*H*-Pyrroles/yield (%)
1	Bn (**2a**)	CO_2Me	None	22	**13a**/71
2			PPTS (1.0)	12	Many products
3	Ph (**2b**)	CO_2Me	PPTS (0.5)	2	**13b**/80
4	Me (**2c**)	CO_2Me	None	57	**13c**/40
5			PPTS (0.5)	18	**13c**/49
6	*sec*-Bu (**2d**)	CO_2Me	None	48	**13d**/57
7			PPTS (0.5)	6.5	**13d**/87
8	*i*-Bu (**2e**)	CO_2Me	None	66	**13e**/27
9			PPTS (0.5)	5	**13e**/80
10	$(CH_2)_2SMe$ (**2f**)	CO_2Me	None	97	**13f**/70
11			PPTS (0.5)	45	**13f**/44
12	Bn (**2a**)	CO_2Et	None	20	**15a**/83
13	Ph (**2b**)	CO_2Et	PPTS (0.5)	3.5	**15b**/quant.
14	*i*-Bu (**2e**)	CO_2Et	PPTS (0.5)	2	**15e**/93

1*H*-Pyrroles **13a**,[10] **13b**,[13] and **13c**[14] are known compounds.



Scheme 4. A plausible pathway from cycloadduct **12** to 1*H*-pyrrole **13**.



Scheme 5. The reaction of functionalized azomethine ylide **3a** with EPP and PA.

tion of **1**, **2a**, and ethyl phenylpropiolate (EPP) gave an almost 2:1 mixture of two regioisomeric 2*H*-pyrroles **17a** and **18a**. Interestingly, the reaction of **1**, **2a**, and phenylacetylene (PA) gave the desired 1*H*-pyrrole **19a** in a moderate yield. Diphenylacetylene (DPA) did not afford any adducts as expected (Scheme 5).

In conclusion, we have reported an effective and versatile preparation method for functionalized 2*H*- and 1*H*-pyrroles, in which the cycloaddition reaction of functionalized azomethine ylides as C-unsubstituted nitrile ylide equivalents with acetylenic dipolarophiles leading to cycloadducts, 2,5-dihydropyrroles, is a key step. The resulting 2,5-dihydropyrroles undergo a fission reaction to give 2*H*-pyrroles and the parent heterocyclic system. The 2*H*-pyrroles unsubstituted at the 3-position undergo a facile isomerization to 1*H*-pyrroles. The one-pot procedure for functionalized 1*H*-pyrroles is also accomplished. Further investigation on this chemistry is now underway in our laboratory.

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8. Structures of 2,5-dihydropyrroles **4a**, **8a**, and **12a** and 1*H*-pyrrole **15a** were confirmed by single crystal X-ray structure analysis and their crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 621689 for **4a**, CCDC 621692 for **8a**, CCDC 621691 for **12a**, and CDDC 621693 for **15a** copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
9. The solution of **4a** (0.350 g, 0.672 mmol) in toluene (5 mL) was heated for 20 h and the solvent was evaporated to dryness, which was subjected to silica-gel column chromatography to afford **10a** (0.180 g, 81%) as an eluent of hexane/ethyl acetate (3:1) and **7** (0.126 g, quant.) as an eluent of hexane/ethyl acetate (1:2), respectively. 2*H*-Pyrrole **10a**: Colorless oil; ^{1}H NMR ($CDCl_3$): 3.50, 3.79 (each 1H, each d, $J = 13.5$ Hz, CH_2Ph), 3.64, 3.71, 3.86 (each 3H, each s, $3 \times OCH_3$), 7.03–7.11 (5H, m, Ph–H), 8.02 (1H, s, 5-H); ^{13}C NMR ($CDCl_3$): 40.25 (*C*H_2Ph), 52.49, 52.81, 53.32 ($3 \times OCH_3$), 92.06 (2-C), 127.10, 127.60, 130.35, 133.15, 135.71, 159.17 (Ph–C and 3- and 4-C), 160.99, 163.02, 163.38 ($3 \times CO_2CH_3$), 166.81 (5-C).
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11. 2*H*-Pyrrole **14a**: ^{1}H NMR ($CDCl_3$): 3.37, 3.54 (each 1H, each d, $J = 13.5$ Hz, CH_2Ph), 3.68, 3.81 (each 3H, each s, $2 \times OCH_3$), 7.11–7.36 (5H, m, Ph–H), 8.04, 8.27 (each 1H, each d, $J = 0.7$ Hz, 5- and 3-H); ^{13}C NMR ($CDCl_3$): 41.44 (*C*H_2Ph), 52.11, 53.07 ($2 \times OCH_3$), 91.27 (2-C), 127.24, 128.03, 128.93, 130.03, 134.29, 135.22 (Ph–C and 3- and 4-C), 160.96, 164.04 ($2 \times CO_2CH_3$), 168.01 (5-C). Chromatographic separation on silica-gel of **14a** from the mixture gave an inseparable mixture of **14a**, **13a**, and other many products due to the decomposition.
12. The solution of **1** (0.143 g, 0.658 mmol) and **2a** (0.213 g, 1.19 mmol) in toluene (1 mL) was heated at 85 °C for 1 h. MP was added to the solution, then the mixture was heated at 85 °C for additional 22 h and the reaction mixture was evaporated to dryness. The residue was subjected to silica-gel column chromatography to afford **13a** (0.128 g, 71%) as an eluent of hexane/ethyl acetate (3:1) and **7** (0.107 g, 86%) as an eluent of hexane/ethyl acetate (1:2), respectively. 1*H*-Pyrrole **13a**: Colorless crystals from hexane–benzene; mp 156–157 °C (lit.[10] 142–143 °C); ^{1}H NMR ($CDCl_3$): 3.79, 3.84 (each 3H, each s, $2 \times OCH_3$), 4.21 (2H, s, CH_2Ph), 7.14 (1H, d, $J = 3.0$ Hz) , 5-H), 7.19–7.24 (5H, m, Ph–H), 8.26 (1H, br, NH); ^{13}C NMR ($CDCl_3$): 32.99, 51.52, 51.55, 112.31, 116.40, 123.02, 127.06, 128.96, 129.00, 137.32, 137.48, 164.49, 165.33.
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15. A similar 1,5-ester group rearrangement was proposed in the course of isomerization of 2*H*-pyrrole to 1*H*-pyrrole derivatives.[3c] Therein, the 2*H*-pyrroles were formed in situ by the DDQ-oxidation of 2,5-dihydropyrroles, which were obtained by the reaction of NH-azomethine ylides with MP. Also, an isomerization process, a sigmatropic rearrangement, of 3*H*-pyrrole to 2*H*- and 1*H*-pyrrole finally through the ester group imigration was discussed: Chiu, P.-K.; Sammes, M. P. *Tetrahedron* **1990**, *46*, 3439–3456; Chiu, P.-K.; Sammes, M. P. *Tetrahedron Lett.* **1987**, *28*, 2775–2778.