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REACTION OF FUNCTIONALIZED AZOMETHINE YLIDES WITH OLEFINIC DIPOLAROPHILES[#]

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[#]Dedicated to Professor Steven M. Weinreb in celebration of his 65th birthday.

Abstract – *N*-Unsubstituted pyrrolidine derivatives are prepared by the cycloaddition of an *N*-unsubstituted azomethine ylide in the pyrido[1,2-*a*]pyrimidin-4(4*H*)-one system and olefinic dipolarophiles. The acid treatment of the cycloadducts, pyrrolidines, caused a fission reaction to give pyrroline derivatives and the parent heterocyclic system.

INTRODUCTION

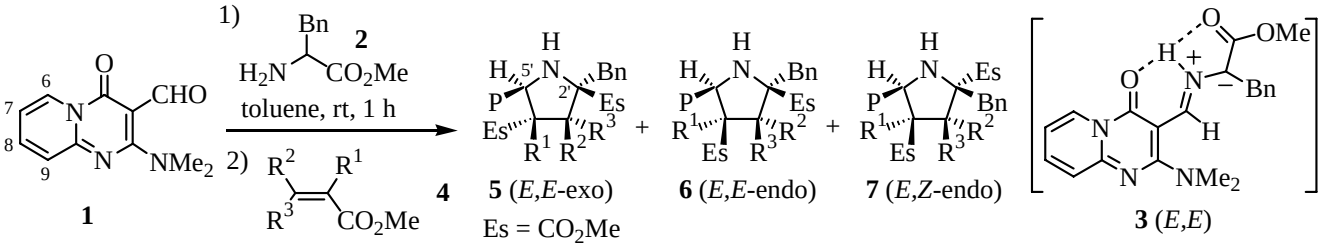
The chemistry on *N*-unsubstituted (NH) azomethine ylides has been attractive due to the biological and pharmacological aspects of the *N*-unsubstituted (NH) pyrrolidines.[1] Recently, we have reported a facile generation of NH-nitrone[2] and NH-azomethine imine[3] from the oxime and hydrazone at the periphery of heterocyclic systems, in which the internal hydrogen bond formation between the NH of the resulting dipoles and the carbonyl oxygen in the heterocycles might facilitate the generation of the dipoles. More recently, we reported the generation of NH-azomethine ylide in the same heterocyclic system under extremely mild conditions and their stereoselective cycloaddition with *N*-phenylmaleimide.[4] Fission reaction of the NH-azomethine ylide cycloadducts under acidic conditions leading to 1-pyrroline derivatives was also discussed. In this paper, we want to report the cycloaddition reaction of the functionalized azomethine ylide with other olefinic dipolarophiles and a novel fission reaction of the cycloadducts to afford pyrroline derivatives and the parent heterocycles.

RESULTS AND DISCUSSION

The reaction of NH-azomethine ylide (**3**), from aldehyde (**1**) and phenylalanine methyl ester (**2**), with

methyl acrylate (**4a**) at room temperature gave three cycloadducts (**5a**) (*E,E-exo*: 62), (**6a**) (*E,E-endo*: 29) and (**7a**) (*E,Z-endo*: 6) in total 73% yield regioselectively and stereoselectively. The similar reaction with methyl methacrylate (**4b**), methyl crotonate (**4c**), dimethyl fumarate (**4d**), dimethyl maleate (**4e**) and dimethyl benzalmalonate (**4f**) gave the corresponding cycloadducts (**5**, **6** and **7**), respectively, in moderate to good total yields.[5] These results are summarized in Table 1. The configuration of the dipole (**3**) participated to the cycloaddition reaction was controlled in a high degree [(*E,E*)-**3**:(*E,Z*)-**3** = 78:22 to >95:5].[6] As demonstrated in Table 1 (entries 1-3 and 6), the regioselectivity in the cycloaddition reaction of **3** to these olefinic dipolarophiles was perfectly controlled to give cycloadducts substituted at the 4'-position by the ester group (entries 1-3 and 6). On the other hand, the stereoselectivity (*exo/endo* selectivity) was not so high; probably steric interaction in their transition states would lead the *exo*-selectivity, but details on the stereoselectivity has been unclear yet.

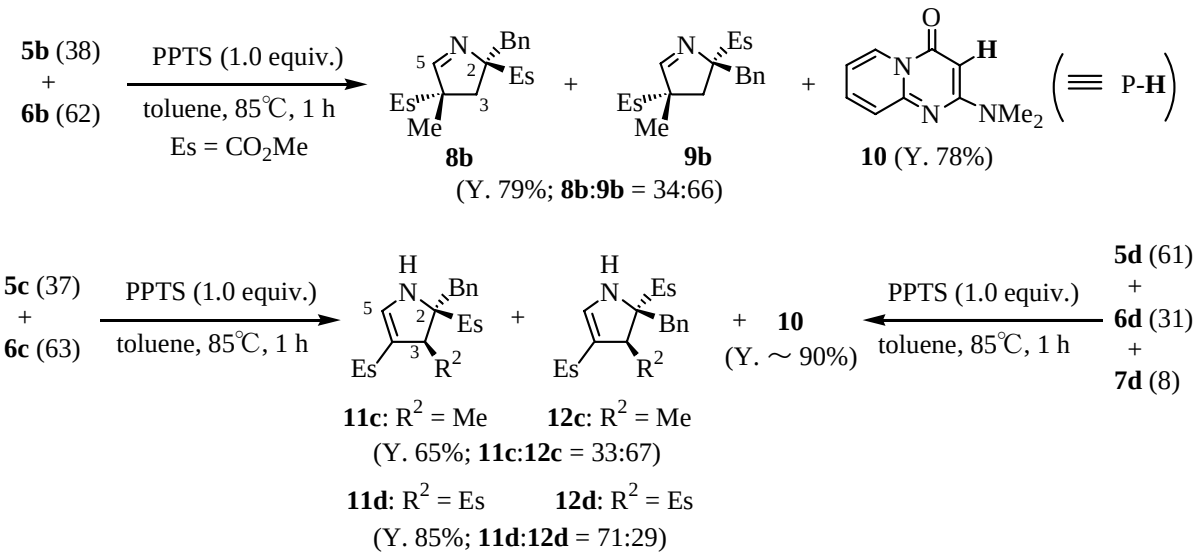
Table 1. Reaction of functionalized azomethine ylide (**3**) with olefinic dipolarophiles (**4**)



Entry	R^1	R^2	R^3	Conditions	Total Yield (%)	Products (Ratio)
1	H	H	H	rt; 20 h	73	**5a** (62), **6a** (29), **7a** (9)
2	Me	H	H	50 °C; 19 h	95	**5b** (39), **6b** (39), **7b** (22)
3	H	Me	H	50 °C; 38 h	74	**5c** (44), **6c** (56), **7c** (9)
4	H	CO_2Me	H	rt; 21 h	94	**5d** (61); **6d** (31); **7d** (8)
5*	H	H	CO_2Me	rt; 46 h	92	**5e** (33), **6e** (77)
6	CO_2Me	H	Ph	50 °C; 48 h	91	**5f** (18), **6f** (82)

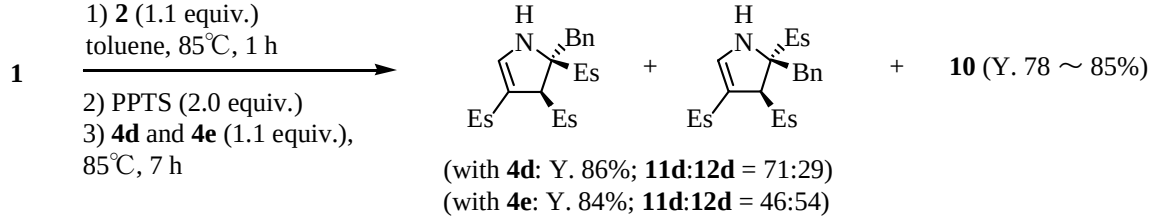
*Small amounts of additional products (<5%) were also detected.

Next our concern was focused to the fission reaction of the cycloadducts under acidic conditions; the treatment of **5a** isolated and the mixture of **5a**, **6a** and **7a** with acids gave an intractable mixture of products. On the other hand, the treatment of the mixture of **5b** (38) and **6b** (62) with pyridinium *p*-toluenesulfonate (PPTS: 1.0 equiv.) in toluene gave 1-pyrroline derivatives (**8b**), (**9b**) and the parent heterocycle (**10**), respectively (Scheme 1). Similar acid treatment of the mixtures of **5c** and **6c** and **5d**, **6d** and **7d** afforded mixtures of 2-pyrrolines (**11c** and **12c** and **11d** and **12d**), respectively.



Scheme 1. Fission reaction of cycloadducts leading to pyrroline derivatives and heterocycle (**10**).

Finally, we examined the 2-pyrroline synthesis in a one-pot procedure; the reaction of aldehyde (**1**), amino ester (**2**), PPTS and dimethyl fumarate (**4d**) and maleate (**4e**) also afforded the desired 2-pyrroline derivatives (**11d**) and (**12d**) in good total yields (Scheme 2).



Scheme 2. One-pot procedure for the preparation of 2-pyrrolines (**11d**) and (**12d**)

In conclusion, we have described an effective preparation method for functionalized pyrrolines, in which the cycloaddition reaction of functionalized azomethine ylides as *C*-unsubstituted nitrile ylide equivalents with olefinic dipolarophiles leading to cycloadducts, pyrrolidines, is a key step.

EXPERIMENTAL[7]

General procedures for the cycloaddition reaction: A solution of aldehyde (**1**) (0.217 g, 1.0 mmol) and (DL)-phenylalanine methyl ester (**2**) (0.197 g, 1.1 mmol) in toluene (2 mL) was heated at 85 °C for 1 h under an aerobic atmosphere. To the solution dipolarophile (1.1 equiv.) was added and the mixture was allowed to react at the indicated temperature and for the indicated time. The mixture was evaporated to dryness, and the residue was crystallized from MeOH to give the corresponding major pyrrolidine. The MeOH solution was evaporated to dryness, and the residue was subjected to a column chromatography on silica gel to give minor pyrrolidines.

Pyrrolidine (5a): Colorless crystals from *i*-PrOH; mp 159-160 °C; ^{1}H NMR ($CDCl_3$): 2.19 (1H, dd, $J_{3'\text{-}4'}$=8.6, J_{gem}=14.5 Hz, 3'-H), 2.94-3.09 (10H, ov, NMe_2, C*H*$_2$Ph, 4'-H and 3'-H), 3.43, 3.77 (each 3H, each s, 2 × CO_2CH_3), 4.07 (1H, br dd, $J_{5'\text{-}4'}$=6.9 [*trans*], $J_{5'\text{-}NH}$=7.0 Hz, 5'-H), 4.56 (1H, br d, NH), 6.84 (1H, dt, *J*=1.0, 6.9 Hz, 7-H), 7.23-7.34 (6H, ov, 9-H and Ph-*H*), 7.55 (1H, ddd, *J*=1.7, 6.6, 8.2 Hz, 8-H), 8.79 (1H, dd, *J*=0.7, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 39.4, 41.6, 44.9, 48.1, 51.8, 52.3, 61.0, 70.0, 93.9, 112.8, 124.5, 126.5, 127.0, 127.9, 130.6, 135.9, 137.4, 148.2, 158.5, 164.5, 173.5, 175.4. Anal. Calcd for $C_{25}H_{28}N_4O_5$ (464.51): C, 64.64; H, 6.08; N, 12.06. Found: C, 64.83; H, 5.94; N, 12.18.

Pyrrolidine (6a): Although this compound could not be isolated as a pure form, the structure was assigned on the basis of its ^{1}H NMR spectroscopic data ($CDCl_3$): 2.29 (1H, dd, $J_{3'\text{-}4'}$=9.6, J_{gem}=13.2 Hz, 3'-H), 2.76 (1H, dd, $J_{3'\text{-}4'}$=9.2, J_{gem}=13.2 Hz, 3'-H), 3.08 (2H, s, C*H*$_2$Ph), 3.18 (6H, s, NMe_2), 3.52, 3.71 (each 3H, each s, 2 × CO_2CH_3), 3.83 (1H, t, $J_{4'\text{-}3'}$=$J_{4'\text{-}5'}$=9.2 Hz, 4'-H), 4.33 (1H, d, $J_{5'\text{-}4'}$=9.2 Hz [*cis*], 5'-H), 6.84 (1H, td, *J*=1.3, 6.9 Hz, 7-H), 7.18-7.29 (6H, ov, 9-H and Ph-*H*), 7.55 (1H, ddd, *J*=1.6, 6.6, 8.9 Hz, 8-H), 8.84 (1H, dd, *J*=0.7, 7.9 Hz, 6-H).

Pyrrolidine (7a): This compound was obtained as a mixture with pyrrolidine (**5a**) in **5a**:**7a**=1:1.9 ratio after a column chromatography on silica gel with hexane/EtOAc (1:1) as an eluent. The selected ^{1}H NMR spectroscopic data of **7a** ($CDCl_3$): 2.61 (1H, dd, $J_{3'\text{-}4'}$=8.3, J_{gem}=13.2 Hz, 3'-H), 2.78 (1H, dd, $J_{3'\text{-}4'}$=7.3, J_{gem}=13.2 Hz, 3'-H), 3.11 (6H, s, NMe_2), 3.26-3.37 (3H, ov, 4'-H and C*H*$_2$Ph), 3.48, 3.68 (each 3H, each s, 2 × CO_2CH_3), 4.50 (1H, d, $J_{5'\text{-}4'}$=9.2 Hz [*cis*], 5'-H), 6.80-6.89 (ov, 7-H (**5a** and **7a**)), 7.18-7.34 (ov, 9-H and Ph-*H* (**5a** and **7a**)), 7.51-7.58 (ov, 8-H (**5a** and **7a**)), 8.78-8.89 (ov, 6-H (**5a** and **7a**)).

Pyrrolidine (5b): Colorless crystals from pentane/CH_2Cl_2; mp 130-131 °C; ^{1}H NMR ($CDCl_3$): 1.01 (3H, s, CH_3), 2.31, 2.77 (each 1H, each d, J_{gem}=13.5 Hz, C*H*$_2$Ph), 2.89 (6H, s, NMe_2), 3.08 (2H, s, 3'-H), 3.58, 3.72 (each 3H, each s, 2 × CO_2CH_3), 4.47 (1H, s, 5'-H), 6.87 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.18-7.32 (4H, ov, 9-H and Ph-*H*), 7.38 (2H, dd, *J*=1.3, 7.6 Hz, Ph-*H*), 7.56 (1H, ddd, *J*=1.7, 6.6, 10.6 Hz, 8-H), 8.88 (1H, dd, *J*=0.7, 6.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 18.0, 41.8, 45.4, 48.4, 51.7, 52.2, 55.9, 64.8, 69.1, 92.8, 113.0, 124.5, 126.2, 127.1, 127.6, 130.6, 135.9, 137.4, 147.9, 159.4, 165.1, 176.0, 176.3. Anal. Calcd for $C_{26}H_{30}N_4O_5$ (478.54): C, 65.26; H, 6.32; N, 11.71. Found: C, 65.10; H, 6.30; N, 11.73. The structure of this compound was confirmed by its X-Ray single crystals analysis.[5]

Pyrrolidine (6b): Colorless crystals from hexane/benzene; mp 197.5-198 °C; ^{1}H NMR ($CDCl_3$): 1.04 (3H, s, CH_3), 1.80, 3.12 (each 1H, each d, J_{gem}=13.5 Hz, C*H*$_2$Ph), 2.93-2.97 (7H, ov, NMe_2 and 3'-H), 3.03 (1H, d, J_{gem}=12.9 Hz, 3'-H), 3.40, 3.74 (each 3H, each s, 2 × CO_2CH_3), 3.79 (1H, br d, $J_{5'\text{-}NH}$=12.9 Hz, 5'-H), 5.30 (1H, br d, $J_{NH\text{-}5'}$=12.9 Hz, NH), 6.84 (1H, ddd, *J*=1.3, 6.6, 6.9 Hz, 7-H), 7.21-7.37 (6H, ov, 9-H and Ph-*H*), 7.55 (1H, ddd, *J*=1.7, 6.6, 8.6 Hz, 8-H), 8.80 (1H, dd, *J*=1.0, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 21.9, 41.7, 46.9, 48.2, 51.8, 52.1, 53.8, 68.8, 69.8, 91.6, 112.8, 124.5, 126.4, 126.9, 127.7, 130.8, 135.8, 137.5, 148.1, 158.9, 165.4, 175.4, 175.9. Anal. Calcd for $C_{26}H_{30}N_4O_7$ (478.54): C, 65.26; H, 6.32; N, 11.71. Found: C, 65.32; H, 6.37; N, 11.74.

Pyrrolidine (7b): Colorless needles from pentane/CH_2Cl_2; mp 165-166 °C; ^{1}H NMR ($CDCl_3$): 1.22 (3H, s, CH_3), 2.26, 3.00 (each 1H, each d, J_{gem}=13.5 Hz, CH_2Ph), 3.06 (6H, s, NMe_2), 3.40, 3.70 (each 3H, each s, 2 × CO_2CH_3), 3.40, 3.47 (each 1H, each d, J_{gem}=13.5 Hz, 3'-H_2), 4.12 (1H, br s, 5'-H), 4.35 (1H, br s, NH), 6.88 (1H, ddd, *J*=1.3, 6.9, 7.3 Hz, 7-H), 7.17-7.37 (6H, ov, 9-H and Ph-*H*), 7.58 (1H, ddd, *J*=1.7, 6.6, 8.9 Hz, 8-H), 8.79 (1H, dt, *J*=1.0, 7.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 24.7, 41.7, 44.4, 46.1, 52.0, 54.7, 68.8, 70.6, 93.6, 113.0, 124.7, 126.6, 126.7, 128.3, 129.7, 135.7, 137.4, 148.0, 159.1, 164.9, 176.3, 176.5. Anal. Calcd for $C_{26}H_{30}N_4O_7$ (478.54): C, 65.26; H, 6.32; N, 11.71. Found: C, 65.20; H, 6.33; N, 11.79. The structure of this compound was confirmed by its X-Ray single crystals analysis.[5]

Pyrrolidine (5c): Colorless crystals from hexane/benzene; mp 151-152 °C; ^{1}H NMR ($CDCl_3$): 1.23 (3H, d, $J_{CH3\text{-}3'}$=6.9 Hz, CH_3), 2.59 (1H, qd, $J_{3'\text{-}CH3}$=$J_{3'\text{-}4'}$=6.9 Hz [*trans*], 3'-H), 3.09, 3.19 (each 1H, each d, J_{gem}=14.2 Hz, CH_2Ph), 3.15 (6H, s, NMe_2), 3.48-3.55 (4H, ov, 4'-H and CO_2CH_3), 3.67 (3H, s, CO_2CH_3), 4.34-4.38 (2H, ov, 5'-H and NH), 6.85 (1H, ddd, *J*=1.3, 6.9, 7.3 Hz, 7-H), 7.15-7.38 (9H, ov, 9-H, Ph-*H* and 1/2C_6H_6), 7.55 (1H, ddd, *J*=1.7, 6.6, 8.6 Hz, 8-H), 8.89 (1H, dd, *J*=0.7, 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 16.5, 41.4, 43.1, 50.8, 51.6, 51.8, 54.1, 60.3, 73.9, 92.8, 112.6, 124.4, 126.2, 127.1, 127.7, 128.3, 130.2, 135.9, 138.2, 148.3, 158.2, 164.4, 173.7, 174.9. Anal. Calcd for $C_{29}H_{33}N_4O_7$ (517.60): C, 62.29; H, 6.43; N, 10.82. Found: C, 67.35; H, 6.58; N, 10.92. The structure of this compound was confirmed by its X-Ray single crystals analysis.[5]

Pyrrolidine (6c): This compound was obtained as a mixture with pyrrolidine (**5c**) in **5c**:**6c**=1:1.7 ratio after a column chromatography on silica gel with hexane/EtOAc (2:1) as an eluent. The selected ^{1}H NMR spectroscopic data of **6c** ($CDCl_3$): 1.35 (3H, d, $J_{CH3\text{-}3'}$=6.9 Hz, CH_3), 2.71, 3.26 (each 1H, each d, J_{gem}=13.9 Hz, CH_2Ph), 3.04 (1H, t, $J_{4'\text{-}3'}$=$J_{4'\text{-}5'}$=10.6 Hz, 4'-H), 3.14-3.22 (7H, ov, NMe_2 and 3'-H), 3.39, 3.68 (each 3H, each s, 2 × CO_2CH_3), 4.78 (1H, d, $J_{5'\text{-}4'}$=10.6 Hz [*cis*], 5'-H), 6.79 (ov, 7-H (**5c** and **6c**)), 7.12-7.38 (ov, 9-H and Ph-*H* (**5c** and **6c**)), 7.52-7.57 (ov, 8-H (**5c** and **6c**)), 8.76 (1H, dd, *J*=0.7, 6.3 Hz, 6-H (**6c**)).

Pyrrolidine (7c): This compound was obtained as a mixture with pyrrolidine (**6c**) in **6c**:**7c**=3:1 ratio after a column chromatography on silica gel with hexane/EtOAc (2:1) as an eluent. The accurate structure of this compound could not be determined because many of its ^{1}H NMR signals were overlapped with **6c**'s signals, however its structure was tentatively assigned to **7** type adduct. The selected ^{1}H NMR spectroscopic data of **7c** ($CDCl_3$): 1.15 (3H, d, *J*=6.9 Hz, CH_3), 3.16 (6H, s, NMe_2), 5.10 (1H, br d, *J*=10.6 Hz, NH).

Pyrrolidine (5d): This compound was obtained as a mixture with pyrrolidine (**6d**) and (**7d**) in **5d**:**6d**:**7d**=10:1:1 ratio after crystallization from MeOH/hexane. Although this compound could not be isolated as a pure form, the structure was assigned on the basis of its ^{1}H NMR spectroscopic data ($CDCl_3$): 3.10 (6H, s, NMe_2), 3.18, 3.26 (each 1H, each d, J_{gem}=13.5 Hz, CH_2Ph), 3.45 (1H, d, $J_{5'\text{-}4'}$=10.6 Hz [*trans*], 5'-H), 3.45, 3.69, 3.75 (each 3H, each s, 3 × CO_2CH_3), 4.07 (1H, d, $J_{3'\text{-}4'}$=10.6 Hz [*trans*], 3'-H), 4.32 (1H, t, $J_{4'\text{-}3'}$=$J_{4'\text{-}5'}$=10.6 Hz, 4'-H), 6.83-6.88 (ov, 7-H (**5d**, **6d** and **7d**)), 7.23-7.40 (ov, 9-H and Ph-*H* (**5d**, **6d** and **7d**)), 7.52-7.59 (ov, 8-H, (**5d**, **6d** and **7d**)), 8.89-8.91 (ov, 6-H, (**5d**, **6d** and **7d**)).

Pyrrolidine (6d): Colorless crystals from hexane/benzene; mp 179-180 °C; ^{1}H NMR ($CDCl_3$): 2.96. 3.11

(each 1H, each d, J_{gem}=14.2 Hz, CH_2Ph), 3.19 (6H, s, NMe_2), 3.41, 3.74, 3.84 (each 3H, each s, 3 × CO_2CH_3), 3.89 (1H, t, $J_{4'-3'}$=$J_{4'-5'}$=9.6 Hz, 4'-H), 4.15 (1H, br d, NH), 4.23 (1H, d, $J_{3'-4'}$=9.6 Hz [*trans*], 3'-H), 4.87 (1H, d, $J_{5'-4'}$=9.6 Hz [*cis*], 5'-H), 6.83 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.15-7.37 (6H, ov, 9-H and Ph-*H*), 7.55 (1H, ddd, *J*=1.7, 6.6, 8.6 Hz, 8-H), 8.76 (1H, d, *J*=6.6 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 37.0, 41.6, 51.7, 51.9, 52.1, 52.4, 56.4, 57.8, 71.3, 94.4, 112.9, 124.5, 126.5, 126.8, 127.9, 130.2, 135.9, 137.0, 148.2, 158.7, 164.0, 172.0, 172.3, 172.5. Anal. Calcd for $C_{27}H_{30}N_4O_7$ (522.55): C, 62.06; H, 5.79; N, 10.72. Found: C, 62.13; H, 5.80; N, 10.74. The structure of this compound was confirmed by its X-Ray single crystals analysis.[5]

Pyrrolidine (7d): This compound was obtained as a mixture with pyrrolidine (**5d**) and (**6d**) in **5d**:**6d**:**7d**=10:1:1 ratio after crystallization from MeOH/hexane. The accurate structure of this compound could not be determined because many of its ^{1}H NMR signals were overlapped with **5d** and **6d**'s signals, however its structure was tentatively assigned to **7** type adduct.

Pyrrolidine (5e): Colorless crystals from *i*-PrOH/benzene; mp 191-192 °C; ^{1}H NMR ($CDCl_3$): 3.06 (2H, s, CH_2Ph), 3.31 (6H, s, NMe_2), 3.51, 3.70 (each 3H, each s, 2 × CO_2CH_3), 3.78-3.80 (4H, ov, CO_2CH_3 and NH), 4.00 (1H, d, $J_{3'-4'}$=9.2 Hz [*cis*], 3'-H), 4.32 (1H, t, $J_{4'-3'}$=$J_{4'-5'}$=9.2 Hz, 4'-H), 4.98 (1H, br d, $J_{4'-5'}$=9.2 Hz [*trans*], 5'-H), 6.81 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.15-7.36 (6H, ov, 9-H and Ph-*H*), 7.52 (1H, ddd, *J*=2.0, 6.6, 8.6 Hz, 8-H), 8.79 (1H, dd, *J*=1.0, 6.9 Hz, 6-H); ^{13}C NMR($CDCl_3$): 40.8, 41.3, 48.3, 51.6, 51.9, 52.6, 55.4, 58.7, 71.8, 92.9, 112.4, 124.5, 126.6, 126.9, 127.8, 130.1, 135.7, 137.1, 148.3, 158.0, 164.2, 172.3, 173.8. Anal. Calcd for $C_{27}H_{30}N_4O_7$ (522.55): C, 62.06; H, 5.79; N, 10.72. Found: C, 61.90; H, 5.83; N, 10.69.

Pyrrolidine (6e): Yellow crystals from *i*-PrOH; mp 169-170 °C; ^{1}H NMR ($CDCl_3$): 2.76 (6H, s, NMe_2), 3.00 (1H, br dd, 4'-H), 3.17, 3.29 (each 1H, each d, J_{gem}=12.9 Hz, CH_2Ph), 3.23 (1H, d, $J_{3'-4'}$=5.6 Hz [*cis*], 3'-H), 3.49, 3.83, 3.84 (each 3H, each s, 3 × CO_2CH_3), 3.56 (1H, dd, $J_{5'-4'}$=4.9 [*cis*], $J_{5'-NH}$=12.5 Hz, 5'-H), 5.49 (1H, br d, $J_{NH-5'}$=12.5 Hz, NH), 6.86 (1H, ddd, *J*=1.3, 6.9, 7.3 Hz, 7-H), 7.27-7.30 (4H, ov, 9-H and Ph-*H*), 7.49 (2H, m, Ph-*H*), 7.56 (1H, ddd, *J*=1.6, 6.6, 8.9 Hz, 8-H), 8.85 (1H, dt, *J*=1.0, 7.3 Hz, 6-H); ^{13}C NMR($CDCl_3$): 41.8, 44.9, 50.4, 51.6, 51.9, 52.7, 53.3, 60.4, 71.1, 92.6, 113.0, 124.5, 126.7, 127.3, 127.9, 131.6, 136.1, 136.4, 148.3, 158.4, 165.1, 170.8, 171.3, 174.5. Anal. Calcd for $C_{27}H_{30}N_4O_7$ (522.55): C, 62.06; H, 5.79; N, 10.72. Found: C, 61.93; H, 5.82; N, 10.61. The structure of this compound was confirmed by its X-Ray single crystals analysis.[5]

Pyrrolidine (5f): This compound was obtained as a mixture with pyrrolidine (**6f**) in 1:1 ratio after a column chromatography on silica gel with hexane/EtOAc (1:1) as an eluent. The selected ^{1}H NMR spectroscopic data of **5f** ($CDCl_3$): 2.51, 2.92 (each 1H, each d, J_{gem}=13.2 Hz, CH_2Ph), 3.11, 3.35, 3.66 (each 3H, each s, 3 × CO_2CH_3), 3.37 (6H, s, NMe_2), 4.82 (1H, s, 3'-H), 5.05 (1H, br d, $J_{NH-5'}$=13.5 Hz, NH), 5.48 (1H, br d, $J_{5'-NH}$=13.5 Hz, 5'-H), 6.78-6.82 (ov, 7-H, (**5f** and **6f**)), 7.09-7.36 (ov, 9-H and Ph-*H* (**5f** and **6f**)), 7.45-7.56 (ov, 8-H, (**5f** and **6f**)), 8.78-8.81 (ov, 6-H, (**5f** and **6f**)).

Pyrrolidine (**6f**): Colorless needles from MeCN; mp 158-159 °C; ^{1}H NMR ($CDCl_3$): 2.97, 3.09, 3.36 (each 3H, each s, 3 × CO_2CH_3), 3.38 (6H, s, NMe_2), 3.65, 3.79 (each 1H, each d, J_{gem}=14.2 Hz, CH_2Ph), 4.59 (1H, s,

3'-H), 4.82 (1H, br d, $J_{NH\text{-}5'}$=13.5 Hz, NH), 5.59 (1H, br d, $J_{5'\text{-}NH}$=13.5 Hz, 5'-H), 6.79 (1H, dt, *J*=1.32, 7.3 Hz, 7-H), 7.13-7.36 (11H, ov, 9-H and Ph-*H*), 7.51 (1H, ddd, *J*=1.7, 6.6, 8.9 Hz, 8-H), 8.79 (1H, dd, *J*=0.7, 7.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 41.7, 45.4, 50.9, 51.7, 52.8, 64.2, 66.2, 70.9, 89.5, 112.1, 124.5, 126.4, 126.5, 127.1, 127.9, 128.3, 129.1, 129.9, 135.5, 137.3, 138.9, 147.7, 160.2, 163.0, 170.0, 170.9, 173.4. Anal. Calcd for $C_{33}H_{34}N_4O_7$ (598.65): C, 66.21; H, 5.72; N, 9.36. Found: C, 66.22; H, 5.68; N, 9.47.

General procedures for fission reaction: A solution of pyrrolidine (0.5 mmol) and PPTS (0.126 g, 0.5 mmol) in toluene (1 ml) was heated at 85 °C for the indicated time under an aerobic atmosphere. The mixture was evaporated to dryness, and the residue was diluted with CH_2Cl_2 (10 mL), neutralized with 5% aqueous $NaHCO_3$ to pH 6-7. The organic layer was dried on anhydrous magnesium sulfate and the solvent was evaporated. The residue was subjected to a column chromatography on silica gel to give the corresponding pyrrolines and heterocyclic moiety (**10**).

General procedures for one-pot reaction: A solution of aldehyde (**1**) (0.109 g, 0.5 mmol) and (DL)-phenylalanine methyl ester (**2**) (0.099 g, 0.55 mmol) in toluene (1 mL) was heated at 85 °C for 1 h under an aerobic atmosphere. To the solution PPTS (0.503 g, 2.0 mmol) was added in twice followed by dipolarophile (1.1 equiv.). The mixture was allowed to react at 85 °C for the indicated time. The mixture was evaporated to dryness, and the residue was portioned between CH_2Cl_2 and 5% aqueous $NaHCO_3$. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was subjected to a column chromatography on silica gel to give the corresponding 2-pyrrolines and heterocyclic moiety (**10**).

1-Pyrrolines (8b and **9b)**: These compounds were obtained as inseparable mixture in **8b**:**9b**=34:66 ratio. colorless oil; ^{1}H NMR ($CDCl_3$): 0.86 (3H, s, CH_3 (**9b**)), 1.36 (3H, s, CH_3 (**8b**)), 1.73 (1H, d, J_{gem}=14.2 Hz, 3-H (**9b**)), 2.22 (1H, d, J_{gem}=14.2 Hz, 3-H (**8b**)), 2.52 (1H, d, J_{gem}=14.2 Hz, 3-H (**8b**)), 2.89 (1H, d, J_{gem}=14.2 Hz, 3-H (**9b**)), 3.09, 3.42 (each 1H, each d, J_{gem}=13.9 Hz, C*H*$_2$Ph (**9b**)), 3.15, 3.24 (each 1H, each d, J_{gem}=14.2 Hz, 3-H (**8b**)), 3.55, 3.74 (each 3H, each s, 2 × CO_2CH_3 (**8b**)), 3.66, 3.71 (each 3H, each s, 2 × CO_2CH_3 (**9b**)), 7.14–7.29 (10H, ov, Ph-*H* (**8b** and **9b**)), 7.38 (1H, s, >CH=N– (**9b**)), 7.47 (1H, s, >CH=N– (**8b**)); ^{13}C NMR ($CDCl_3$): 21.3, 22.6, 39.5, 39.6, 43.6, 44.0, 52.2, 52.3, 60.4, 60.5, 84.6, 126.5, 126.7, 127.8, 130.4, 130.6, 135.4, 135.5, 168.1, 173.0, 173.4, 173.5.

2-Pyrrolines (11c and **12c)**: These compounds were obtained as inseparable mixture in **11c**:**12c**=33:67 ratio. colorless oil; ^{1}H NMR ($CDCl_3$): 1.10 (3H, d, $J_{CH3\text{-}3}$=6.6 Hz, CH_3(**11c**)), 1.29 (3H, d, $J_{CH3\text{-}3}$=6.9 Hz, CH_3 (**12c**)), 2.95-3.09 (3H, ov, 3-H(**11c**), C*H*$_2$Ph(**11c**) and C*H*$_2$Ph (**12c**)), 3.1-3.23 (2H, ov, C*H*$_2$Ph (**11c**) and C*H*$_2$Ph (**12c**)), 3.42 (1H, q, $J_{3\text{-}CH3}$=6.9 Hz, 3-H (**12c**)), 3.62, 3.65 (each 3H, each s, 2 × CO_2CH_3 (**12c**)), 3.68, 3.73 (each 3H, each s, 2 × CO_2CH_3 (**11c**)), 4.55 (2H, ov, NH (**11c** and **12c**)), 7.03-7.10 (4H, ov, Ph-*H* (**11c** and **12c**)), 7.13-7.15 (2H, ov, Ph-*H* (**11c**)), 7.23-7.31 (5H, ov, Ph-*H* (**12c** and **11c**) and >CH=N– (**11c**)), 7.35 (1H, s, >CH=N– (**12c**)).

2-Pyrroline (11d): Colorless oil; ^{1}H NMR ($CDCl_3$): 3.05, 3.26 (each 1H, each d, J_{gem}=13.2 Hz, CH_2Ph), 3.65, 3.67, 3.70 (each 3H, each s, 3 × CO_2CH_3), 3.92 (1H, br s, 3-H), 4.92 (1H, br d, $J_{NH\text{-}5}$=2.0 Hz, NH), 7.06-7.10 (2H, ov, Ph-*H*), 7.26-7.30 (3H, ov, Ph-*H*), 7.31 (1H, br d, $J_{5\text{-}NH}$=2.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$): 46.1, 50.8, 52.3, 52.5, 56.2, 75.4, 101.7, 127.6, 128.5, 129.7, 134.2, 147.5, 165.2, 171.4, 172.1.

2-Pyrroline (12d): Colorless oil; ^{1}H NMR ($CDCl_3$): 2.93, 3.31 (each 1H, each d, J_{gem}=12.9 Hz, CH_2Ph), 3.66, 3.70, 3.82 (each 3H, each s, 3 × CO_2CH_3), 4.24 (1H, d, $J_{3\text{-}5}$=1.0 Hz, 3-H), 4.77 (1H, br d, $J_{NH\text{-}5}$=3.0 Hz, NH), 7.07-7.10 (2H, m, Ph-*H*), 7.24-7.30 (3H, ov, Ph-*H*), 7.32 (1H, br d, $J_{5\text{-}NH}$=3.0 Hz, 5-H); ^{13}C NMR ($CDCl_3$): 40.2, 50.8, 52.2, 52.8, 53.4, 74.1, 103.5, 127.5, 128.7, 129.3, 134.7, 148.6, 165.1, 170.7, 173.6.

REFERENCES AND NOTES

1. U. Obst, P. Betschmann, C. Lemer, P. Seiler, and F. Diederich *Helv. Chim. Acta*, 2000, **83**, 855. (b) W. H. Pearson, In *Studies in Natural Products Chemistry*; ed. by Atta-Ur-Rahman; Elsevier: New York, 1998; Vol. 1, 323-358. (c) G. W. Gribble, In *Comprehensive Heterocyclic Chemistry*; ed. by A. R. Katritzky, C. W. Rees and E. F. V. Scriven; Pergamon: Oxford, U. K., 1996; Vol. 2, 207-257.
2. M. Shirai, H. Kuwabara, S. Matsumoto, H. Yamamoto, A. Kakehi, and M. Noguchi *Tetrahedron*, 2003, **59**, 4113.
3. M. Noguchi, S. Matsumoto, M. Shirai, and H. Yamamoto *Tetrahedron*, 2003, **59**, 4123.
4. K. Kawashima, A. Kakehi, and M. Noguchi submitted to *Tetrahedron*.
5. The structures of cycloadducts (**5**, **6** and **7**) were characterized by their spectroscopic data. Moreover, the structures of five key cycloadducts (**5b**, **7b**, **5c**, **6d** and **6e**) were confirmed by single crystal X-Ray analysis and crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 622532 for **5b**, CCDC 622531 for **7b**, CCDC 622529 for **5c**, CCDC 622530 for **6d** and CCDC 622533 for **6e**. 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).
6. The calculation results of the dipoles of (*E*,*E*)-**3** and (*E*,*Z*)-**3** by PM3 indicated that the interconversion between these dipoles could be ruled out.
7. The general experimental procedures were the same as those reported in lit.4.