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[3+2] CYCLOADDITIONS OF INDOLENINE-DERIVED AZOMETHINE YLIDES A RAPID ENTRY INTO PYRROLO [1,2-a] INDOLINES.

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Summary : Non-stabilised azomethine ylides, produced by fluoride-induced desilylation of N-trimethylsilylmethyl indolium salts, undergo rapid cycloaddition with electron deficient dipolarophiles to yield adducts containing the pyrrolo [1,2-a] indoline ring system.

Recently, the synthetic utility of 1,3-dipoles has been greatly enhanced by the development of convenient methods for the generation and subsequent trapping of reactive non-stabilised azomethine ylides[1]. In particular, fluoride induced desilylation of N-trimethylsilylmethyl immonium salts has provided rapid access to imidate and thioimidate-methylides[2]. Additionally this approach has been extended to the generation of heterocyclic-based azomethine ylides derived from thiazolium[3] and indole[4] precursors.

We now report that the pyrrolo [1,2-a] indoline nucleus **4**, which is a central feature of the mitomycin class of antitumour antibiotics[5], is readily accessible from cycloaddition of azomethine ylides derived from N-trimethylsilylmethyl indolium salts **2**.

In a typical experiment, treatment of **1**(6.28mmol), with trimethylsilylmethyl triflate (6.28mmol), in dichloromethane (15ml), yielded the salt **2** (6.09mmol 97%), as a purple solid after trituration in ether. After heating a solution of **2** (0.5mmol), N-phenylmaleimide (0.5mmol) and caesium fluoride (0.6mmol), in acetonitrile (5ml), at 60°C for 15 mins, t.l.c. examination indicated complete reaction. Aqueous work-up followed by chromatography on silica[6] (EtOAc / hexane 1 : 4) yielded **6a** and **6b** (2:1 combined yield 70%) presumably resulting from cycloaddition of maleimide to azomethine ylide **3.** The results of similar cycloadditions are summarised in table 1[7].

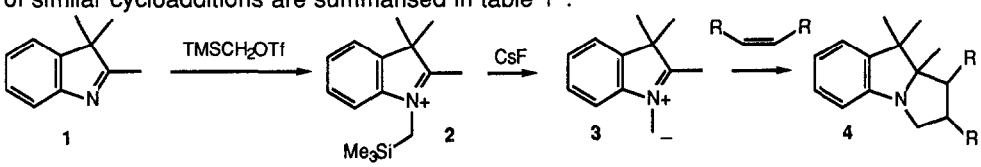
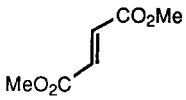
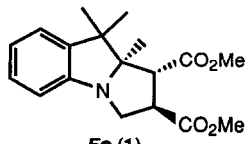
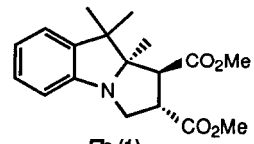
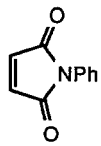
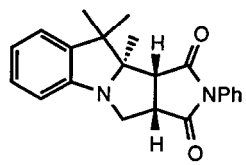
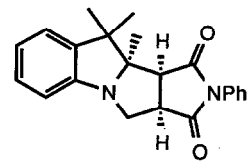
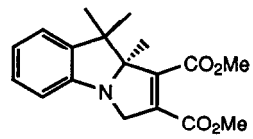
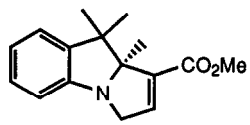
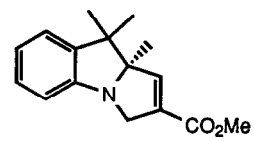
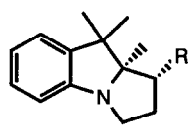
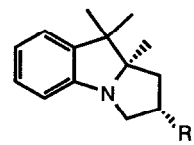


table 1. [3+2] cycloadditions of azomethine ylide **3**

entry	dipolarophile	product(s)[a]		conditions temp °C / time min		isolated yield (%)
1		 **5a** (1)	 **5b** (1)	60	20	50[b]
2		 **6a** (2)	 **6b** (1)	60	15	70
3		 **7**		60	15	75
4		 **8a** (1.5) (1)	 **8b** (1) (-)	60 0	20 30	75 40
						
5	R = COMe	**9a** (1)	**9b** (-)	60	30	32
6	R = CN	**10a** (-) (1)	**10b** (1) (1)	60 20	25 30	51 30[b]
7	R = CO_2Me	**11a** (7) (-)	**11b** (2) (1)	60 20	15 15	50 40

(a): Ratio of isomers is described in parentheses. All new compounds gave i.r., n.m.r., and mass spectral data which was consistent with the proposed structures.

(b): It was not possible to separate these isomers by chromatography and the ratio in this case was determined from the n.m.r. spectrum of an isomeric mixture.

In addition, polycyclic adducts **14** were formed from the tetrahydrocarbazole derivative **12**. Alkylation and desilylation is assumed to generate the ylide **13**, which undergoes cycloaddition with electron deficient dipolarophiles to give the products shown in table 2.

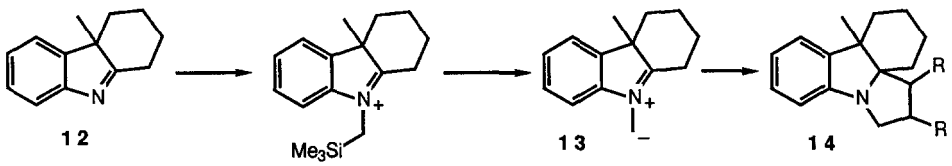
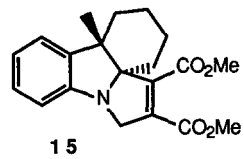
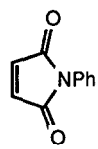
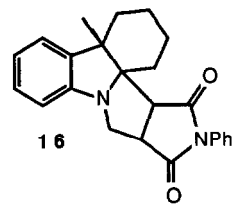


table 2. [3+2] cycloadditions of azomethine ylide **13**

entry	dipolarophile	product	conditions temp °C / time min		isolated yield (%)
1		 **15**	60	40	57
2		 **16**	60	15	23[a]

(a): Product isolated as a 1:1 mixture of diastereoisomers

A number of points are noteworthy; (i) Cycloadditions were only successful with electron deficient dipolarophiles; all attempts to obtain cycloadducts from non-activated or electron rich dipolarophiles failed. (ii) The regioselectivity of cycloadditions involving non-symmetrical dipolarophiles is temperature dependent. (iii) All cycloadditions are highly stereoselective and favour formation of the isomer resulting from an *exo* transition state.

Further studies directed towards the utilisation of this approach in the synthesis of natural products are in progress.

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References and Notes

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7. The structures of all cycloadducts were determined using a combination of high field NMR techniques. Representative data are shown below. Full details will be published in due course.

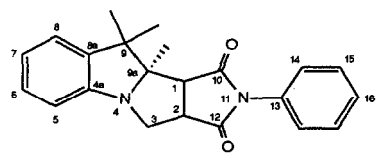
   Adduct 6a; ^{1}H NMR (400 MHz, $CDCl_3$), δ : 1.19 (3H, s, C9-Meα), 1.37 (3H, s,C9a-Meα), 1.63 (3H, s, C9-Meβ), 3.43 (1H, m, C2-Hβ), 3.44 (1H, m, C1-Hβ), 3.59 (1H, m, C3-Hα), 4.10 (1H, m, C3-Hβ), 6.73 (1H, d, C5-H), 6.95 (1H, t, C7-H), 7.15 (1H, d, C8-H), 7.17 (1H, d, C6-H), 7.28 (2H, d, C14-H), 7.39 (1H, t, C16-H), 7.47 (2H, t, C15-H).

   Adduct 6b; 1.20 (3H, s, C9-Meα), 1.37 (3H, s, C9a-Me),1.89 (3H, s, C9-Meβ), 3.09 (1H, d, C1-Hα), 3.48 (1H,ddd, C2-Hα), 3.64 (1H, dd,C3-Hα), 4.19 (1H, dd, C3-Hβ), 6.47 (2H, d, C14-H), 6.69 (1H, d, C5-H), 6.91(1H, t, C7-H), 7.08 (1H, t, C6-H), 7.09 (1H, d, C8-H), 7.25 (1H, t, C16-H), 7.27 (2H, t, C15-H).

   Adduct 8a; 1.00 (3H, s, C9-Meβ), 1.48 (3H, s, C9a-Meα), 1.52 (3H, s, C9-Meα), 3.81 (3H, s, OMe), 3.96 (1H, dd, C3-Hβ), 4.40 (1H, dd, C3-Hα), 6.69 (1H, d, C5-H), 6.83 (1H, t, C2-H), 6.87 (1H, t, C7-H), 7.01 (1H, d, C8-H), 7.13 (1H, t, C6-H).

   Adduct 8b; 1.24 (3H, s, C9-Meα), 1.35 (3H, s, C9a-Meα), 1.38 (3H, s, C9-Meβ), 3.72 (3H, s, OMe), 4.22 (1H, dd, C3-Hβ), 4.28 (1H, dd, C3-Hα), 6.77 (1H, d, C5-H), 6.88 (1H, t, C7-H), 6.95 (1H, dd, C1-H), 7.00 (1H, d, C8-H), 7.13 (1H, t, C6-H).

   Adduct 10b; 1.15 (3H, s, C9-Meα), 1.32 (3H, s, C9-Meβ), 1.38 (3H, d, C9a-Meα), 1.78 (1H, dd, C1-Hα), 1.98 (1H, ddq, C1-Hβ), 2.87 (1H, dddd, C2-Hβ), 3.53 (1H, dd, C3-Hα) 4.00 (1H, dd, C3-Hβ), 6.62 (1H, d, C5-H), 6.86 (1H, t, C7-H), 7.05 (1H, d, C8-H), 7.10 (1H, t, C6-H).



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