EFFECT OF ELECTRON-WITHDRAWING SUBSTITUENTS ON THE INVERSE-ELECTRON DEMAND DIELS-ALDER REACTION OF 2-AMINOPYRROLES AND 1,3,5-TRIAZINES

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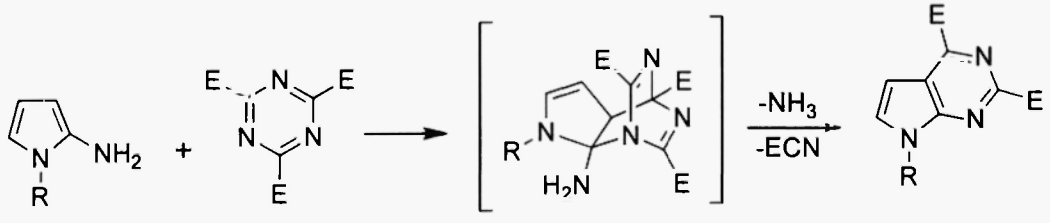
Abstract: Inverse-electron demand Diels-Alder reactions of 1,3,5-triazines and 2-aminopyrroles are facilitated by electron-withdrawing groups (EWG) on both reactants. Whereas HOMO-LUMO calculations predict that EWG on 2-aminopyrroles should lower the relative rate of reaction. This apparent contradiction can be explained if the reaction cascade is under equilibrium control with at least one reversible step.

Introduction

The 2-aminopyrrole ring is very electron rich. Only derivatives with electron withdrawing substituents are stable.[1] Simple 2-aminopyrroles, without further substitution on the ring, have been isolated as their tetraphenylborate salts.[2] Addition of triethylamine (TEA) to solutions of the tetraphenylborate salts can be used to generate simple 2-aminopyrroles *in situ*. In this manner the Diels-Alder reaction of 2-aminopyrroles with dimethyl acetylenedicarboxylate (DMAD) was attempted but Michael addition occurred instead.[3] Dang and co-workers have examined the inverse electron-demand Diels-Alder (IDA) reactions of 1,3,5-triazines with 4-cyano-2-aminopyrroles.[4,5] A cascade reaction took place with the formation of pyrrolo[2,3-*d*]pyrimidines. Theoretical studies of this process have also appeared.[6,7] In this communication we examine how the nature of the substituents on the 1,3,5-triazines and 2-aminopyrroles affect the reaction.



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2a (E=CO_2Et)
2b (E=CF_3)

3(R=CH_3; E=CO_2Et)
4(R=C_2H_5; E=CO_2Et)
5(R=*t*-C_4H_9; E=CO_2Et)
6(R=CH_3; E=CF_3)
7(R=C_2H_5; E=CF_3)
8(R=*t*-C_4H_9; E=CF_3)

Results and Discussion

The reaction of 2-aminopyrroles **1** (R = CH_3, C_2H_5 and *t*-C_4H_9) with six symmetrical 1,3,5-triazines **2** (E = CO_2Et, CF_3, Cl, OCH_3, Ph and H) was studied.[8] Reactions were carried out in THF by adding the 2-aminopyrrole tetraphenylborate salt and TEA to the solvent (forming **1**) and then adding the 1,3,5-triazine **2**.[9] Products were isolated by column chromatography and identified by ^{1}H NMR spectroscopy and high resolution mass spectroscopy.[10] When the triazine substituent (E) was either the ethoxycarbonyl **2a** or trifluoromethyl **2b** group the pyrrolo[2,3-*d*]pyrimidine was formed. No reaction was observed with E = H, Cl, OCH_3 or phenyl. Table-1 summarizes the reaction conditions and yields.

Table-1 : Reaction conditions and product yields

R	E	**1**:**2**:TEA[a]	Solv.	Temp.	Time	Yield (%)[e]
CH_3	CO_2Et	1:1.50:1.50	THF	25°C	2.5 h	40
C_2H_5	CO_2Et	1:1.75:1.75	THF	25°C	17 h	23
t-C_4H_9	CO_2Et	1:1.75:1.75	THF	25°C	1 h	78
CH_3	CF_3	1:1.75:1.75	THF	25°C	<5 min[c]	(40)
C_2H_5	CF_3	1:1.75:1.75	THF	25°C	25.5 h	(25)
t-C_4H_9	CF_3	1:1.75:1.75	THF	25°C	25 h	(40)
CH_3	CF_3	1:1.1:3.0	EMIM[b]	55-60°C	48 h	21
C_2H_5	CF_3	1:1:0.5	THF	25°C	96 h	23
t-C_4H_9	CF_3	1:1:0.5	THF	25°C	17 h	61(77)
CH_3	OCH_3	1:1:1	THF	reflux	23 h	NR[d]
CH_3	OCH_3	1:1.15:1.15	DMSO	25°C	216 h	NR[d]
CH_3	Cl	1:1.15:1.15	DMSO	25°C	20 h	NR[d]
CH_3	Ph	1:1:3.0	EMIM[b]	25°C	48 h	NR[d]
CH_3	Ph	1:1.15:1.15	DMSO	25°C	24 h	NR[d]
CH_3	H	1:1:1	THF	25°C	72 h	NR[d]

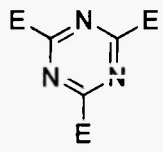
[a]Ratio of mmoles
[b] Product sublimed and reaction was in run in a sublimator in the ionic liquid 1-ethyl-3-methyl-1*H*-imidazolium tetrafluoroborate (EMIM).
[c]No starting salt or 2-aminopyrrole was detectable by ^{1}H NMR immediately after mixing.
[d]No reaction
[e]Isolated yields. Values in parenthesis determined by ^{1}H NMR using 1,4-dimethoxybenzene as the internal standard.

IDA reactions are under $LUMO_{diene}$ control.[5] This suggested the possibility that the $LUMO_{diene}$ energies of the unreactive 1,3,5-triazines are not sufficiently negative. HOMO and LUMO energies (Table-2) of the 1,3,5-triazines and 2-aminopyrroles used were calculated using AM1 optimized geometries (Hyperchem 7.5). These results would seem to confirm that the $LUMO_{diene}$ energy controls the process, given that those 1,3,5-triazines whose LUMO energies were less negative than that of the 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine **2a** did not react. It can also be seen in the $HOMO_{1a}$-$LUMO_2$ differences. Reaction did not take place when this difference was more negative than -6.5 eV.

The results of the current study can be compared to those obtained by Dang.[4] Whereas this study found that the parent 1,3,5-triazine (E = H) did not react; they observed a slow reaction between 2-amino-4-cyanopyrroles and 1,3,5-triazine — a result that suggested that 2-amino-4-cyanopyrroles were more reactive than simple 2-aminopyrroles. Cyano groups are electron withdrawing. Therefore 2-amino-4-cyanopyrroles are expected to be less electron rich than simple 2-aminopyrroles and hence less reactive; contrary to what has been observed. HOMO and LUMO values and $HOMO_9$-$LUMO_2$ differences (Table-2) were calculated for the model compound 1-methyl-2-amino-4-cyanopyrrole **9**. Based on

its HOMO value, 4-cyano-2-aminopyrroles would be expected to be less reactive than simple 2-aminopyrroles in any IDA reaction. Further, based on the $HOMO_9$-$LUMO_2$ differences, 4-cyano-2-aminopyrroles would also not be expected to react with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine **2a** as reported.[4]

Table-2. HOMO and LUMO values of 1,3,5-triazines and 2-aminopyrroles



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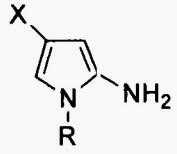

1a (R=CH_3, X=H); **9** (R=CH_3, X=CN)

E	HOMO (eV)	LUMO (eV)	R	X	HOMO (eV)	LUMO (eV)	$HOMO_{1a}$-$LUMO_2$ (eV)	$HOMO_9$-$LUMO_2$ (eV)
CF_3	-12.888	-2.389	CH_3	H	-7.986	1.287	-5.597	-6.137
CO_2Et	-11.691	-1.477	CH_3	CN	-8.526	0.518	-6.510	-7.049
Cl	-11.644	-1.311					-6.675	-7.215
C_6H_5	-9.639	-0.730					-7.256	-7.796
H	-11.318	-0.552					-7.435	-7.974
OCH_3	-10.629	-0.161					-7.826	-8.365

HOMO-LUMO differences can be used to predict relative rates only in reactions under kinetic control. Mechanistic studies, currently underway, indicate that at least one of the steps leading to the pyrrolo[2,3-*d*]pyrimidines **3-8** may be reversible. This would be analogous to recent IDA studies with 1,2,4-triazines[11] and 1,2,4,5-tetrazines[12] where it was reported that the first step of the reaction was reversible and the possibility that a subsequent step was also reversible could not be eliminated. If one or more of the steps leading to the final cycloaddition product was reversible, then HOMO-LUMO differences could not be used to accurately predict relative rates.

Acknowledgements

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9 To 1.0 mL of a THF solution containing 0.218 mmol of the 2-aminopyrrole tetraphenylborate salt (2) there was added 0.109 mmol of Et_3N and then 0.218 mmol of triazine **2**. The reaction was run in the dark, under nitrogen, with constant stirring. At the end of the reaction the solvent was removed with a stream of nitrogen gas and the residue was dissolved in the appropriate solvent for column chromatography on silica gel (**3**: CH_2Cl_2/EtOAc 1:3; **5**: EtOAc /$CHCl_3$1:1; 4,7 and 8: EtOAc/$CHCl_3$ 3:1. The dark blue fluorescent product (TLC) was isolated in each reaction. Pyrrolo[2,3-d]pyrimidine **5** was recrystallized from EtOH and water, and pyrrolo[2,3-*d*]pyrimidine 4 was recrystallized from $CHCl_3$ and petroleum ether. Isolated pyrrolo[2,3-*d*]pyrimidines **3**, 7 and **8** were re-chromatographed. All products were dried under reduced pressure for 24 hrs and found to be pure by 300 MHz proton NMR in $CDCl_3$. Pyrrolo[2,3-*d*]pyrimidine 6, obtained from the reaction of 1-methyl-2-aminopyrrole and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**2b**), sublimed during its formation. The reaction was carried out at 55-60 °C under a static blanket of N_2, in the ionic liquid 1-ethyl-3-methyl-1*H*-imidazolium tetrafluoroborate (EMIM) and 6 was isolated by sublimation

10 2,4-Bis(ethoxycarbonyl)-7-methylpyrrolo[2,3-*d*]pyrimidine **3**: mp 120-121°C; ^{1}H NMR (300 MHz): δ 7.54 (d, 1H, J = 3.7 Hz), 7.15 (d, 1H, J = 3.7 Hz), 4.56 (m, 4H), 4.03 (s, 3H), 1.50 (m, 6H); HRMS (M+H) expected 278.1141, experimental 278.1133. 2,4-Bis(ethoxycarbonyl)-7-ethylpyrrolo[2,3-*d*]pyrimidine **4**: mp 74.5-75°C; ^{1}H NMR (300 MHz): δ 7.61 (d, 1H, J = 3.7 Hz), 7.16 (d, 1H, J = 3.7 Hz), 4.53 (m, 6H), 1.51 (m, 9H); HRMS (M+H) expected 292.1297, experimental 292.1300. 2,4-Bis(ethoxycarbonyl)-7-t-butylpyrrolo[2,3-*d*]pyrimidine **5**: mp 72°C; ^{1}H NMR (300 MHz): δ 7.71 (d, 1H, J = 3.7 Hz), 7.09 (d, 1H, J = 3.7 Hz), 4.55 (m, 4H), 1.87 (s, 9H), 1.50 (m, 6H) ; HRMS (M+H) expected 320.1610, experimental 320.1603. 2,4-Bis(trifluoromethyl)-7-methylpyrrolo[2,3-*d*]pyrimidine 6: mp 97-99°C (sealed tube); ^{1}H NMR (300 MHz): δ 7.56 (d, 1H, J = 3.6 Hz), 6.86 (b, 1H), 4.02 (s, 3H) ; HRMS (M+H) expected 270.0466, experimental. 2,4-Bis(trifluoromethyl)-7-ethylpyrrolo[2,3-*d*]pyrimidine 7: mp 56°C; ^{1}H NMR (300 MHz): δ 7.61 (d, 1H, J = 3.7 Hz), 6.86 (dq, 1H, J = 3.7 Hz, JHF=1.85 Hz), 4.47 (q, 2H, J = 7.4 Hz), 1.56 (t, 3H, J = 7.4 Hz) ; HRMS (M+H) expected 284.0622, experimental 284.0620. 2,4-Bis(trifluoromethyl)-7-*t*-butylpyrrolo[2,3-*d*]pyrimidine **8**: oil; ^{1}H NMR (300 MHz): δ 7.73 (d, 1H, J = 3.7 Hz), 6.79 (dq, 1H, J = 3.7 Hz, J_{HF} = 1.85 Hz), 1.85 (s, 9H) ; HRMS (M+H) expected 312.0935, experimental 312.0932

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