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Studies on inverse electron demand hetero Diels–Alder reaction of perfluoroalkyl 2(1H) pyridones with different dienophiles under microwave irradiation☆

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Abstract

The reaction of *N*-acetyl perfluoroalkyl substituted 2(1H) pyridones (**7**) with dimethylacetylenedicarboxylate (DMAD) on neutral alumina under solvent free microwave irradiation conditions extended to undergo an inverse electron demand hetero Diels–Alder reaction, however resulted exclusively in *E*, *Z* isomers (3:1) of Michael-type N-adducts (**8**). The similar reaction in case of **7a** under thermal and photochemical conditions also gave the same products.

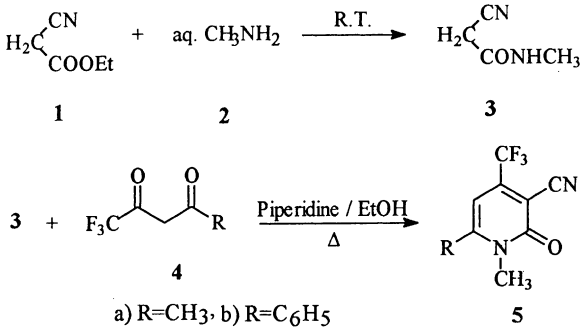
Keywords: N-substituted 2(1H) pyridones; DMAD; N-adducts

1. Introduction

The 2(1H) pyridones are known to have aromaticity and conjugated diene properties possible for Diels–Alder reaction [1]. The cycloaddition products of 2(1H) pyridones and dienophiles have an isoquinoline skeleton, found in many natural products and also have great potential as synthetic intermediates [2]. Earlier reports [3,4], reveal that N-unsubstituted 2(1H) pyridones on reaction with different dienophiles resulted in Diels–Alder cycloadducts and also formation of aromatics by loss of isocyanate from the cycloadduct. Hongo and co-workers [5] reported that, N-substituted 2(1H) pyridones having electron withdrawing groups when reacted with maleic anhydride gave the Diels–Alder cycloadducts. Considering the importance of 2(1H) pyridones as dienes in Diels–Alder reactions and our continued interest in the synthesis of 2(1H) pyridones and their reactions prompted us to study the cycloaddition reaction of 2(1H) pyridones with different dienophiles. Thus *N*-methyl, *N*-acetyl and N-unsubstituted 2(1H) pyridones [6] having perfluoroalkyl groups have been prepared and reacted with different dienophiles. The outcome of the study is mainly the formation of *E* and *Z* isomers of 2(1H) pyridone N-adducts and is reported here for the first time.

2. Results and discussion

The cyanoethylacetate (**1**) was reacted with an aqueous solution of methylamine (**2**) to result in the formation of *N*-methyl cyanoacetamide (**3**). The resultant compound (**3**) on cyclisation with unsymmetrical 1,3 di-ketones (**4**) gave regioselectively one isomer, i.e. *N*-methyl-3-cyano-4-trifluoromethyl-6-substituted 2(1H) pyridones (**5**) as reported earlier [7]. This has been also proved in an earlier report [8] on the synthesis of 4-trifluoromethyl-2(1H) pyridone derivatives. It is found that the *N*-methyl group in compound **3** has no influence on the orientation of reaction to give the alternate regioisomer of compound **5**.



In order to utilise compounds (**5**) as dienes for Diels–Alder reaction they were reacted with several dienophiles such as dimethylacetylenedicarboxylate (DMAD), maleic anhydride and *N*,*N*-dimethyl substituted stilbene esters.

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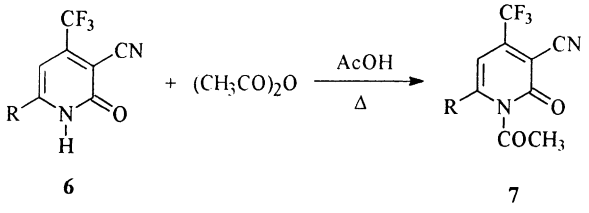
under microwave irradiation. However, no new product is formed. It is presumed that the methyl group which is present on nitrogen in 2(1H) pyridones (**5**) further enhances the participation of the non-bonded electrons of nitrogen in delocalization reducing diene character. Therefore the *N*-unsubstituted 2(1H) pyridones (**6**) were acylated with acetic anhydride to trap the non-bonded electrons on nitrogen and found to give selective formation of *N*-acetyl 2(1H) pyridones (**7**) in good yields. Our earlier studies on the alkylation [9] of 2(1H) pyridones with bromoethylacetate [10], allylbromide [11] and 2-chloroacetone [12] resulted selectively in O-alkylated products, whereas the acetylation resulted in only *N*-acetyl compounds (**7**).



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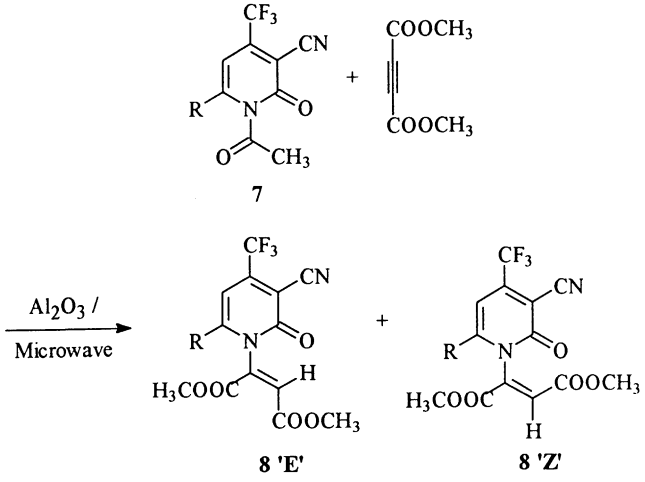
R) = a) C_6H_5, b) p-$CH_3C_6H_4$, c) p-ClC_6H_4, d) CH_3

The compounds (**7**) were reacted with DMAD on neutral alumina under solvent free microwave irradiation conditions in order to undergo inverse electron demand hetero Diels–Alder reaction. However the resultant products are found to be *E, Z* isomers of Michael-type N-adducts (**8**) in the ratio (3:1).

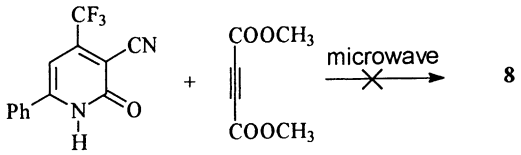


A similar reaction was performed for **7a** under thermal conditions using toluene as solvent and also under photochemical condition with acetonitrile as medium. In all the cases the products (**8**) were found to be formed in the same proportion. The products are tabulated in the Table 1.

Initially it is believed that the compounds (**7**) were losing ketene to form 2(1H) pyridones (**6**) in situ and reacting with DMAD to resultant products (**8**). However when compound **6a** was reacted with DMAD under microwave irradiation condition, there was no formation of any product except to recover the starting material. This shows that the formation of products (**8**) are not from compound (**6**).

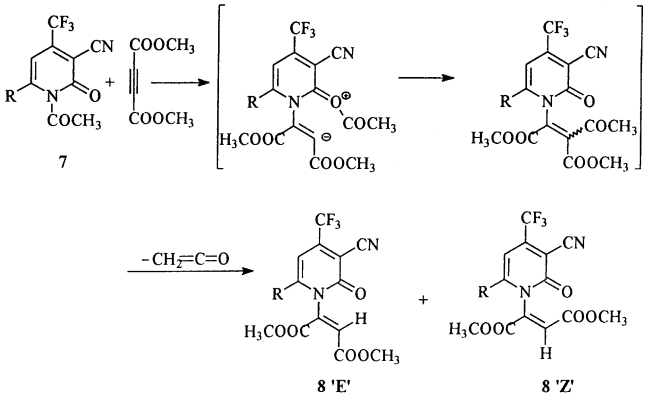
Table 1

Compound no.	R	Yield (%)	8 (*E* + *Z*)
5a	CH_3	56	
5b	C_6H_5	55	
7a	C_6H_5	55	
7b	*p*-$CH_3C_6H_4$	54	
7c	*p*-ClC_6H_4	58	
7d	CH_3	46	
8a	C_6H_5		(33 + 11)
8b	*p*-$CH_3C_6H_4$		(34 + 15)
8c	*p*-ClC_6H_4		(28 + 9)
8d	CH_3		(37 + 12)



6a

The literature [13] suggests that the *N*-acyl group in 2(1H) pyridones readily undergoes migration on to oxygen. Therefore, it is concluded that the *N*-acyl group migrated on to oxygen in situ as reported in previous work [13] and reacts with DMAD. Therefore, the mechanism is formulated for the formation of products (**8**) as follows.



The structures of products (**8**) was established based on spectroscopic data and are comparable with analogous compounds [14]. Similarly the reaction of (**7**) with other dienophiles such as maleimide, maleic anhydride, *N*,*N*-dimethyl substituted stilbene esters on microwave irradiation and ethyl vinylether, acrylonitrile under thermal condition failed to give any products.

2.1. Conclusion

The attempted inverse electron demand hetero Diels–Alder reaction of perfluoroalkyl *N*-acetyl 2(1H) pyridones

with DMAD under three sets of conditions such as microwaves, thermal and photochemical did not occur; only *E, Z* isomers of Michael-type N-adducts were formed.

3. Experimental

3.1. General

Melting points were determined in open glass capillaries on a Mettler FP 51 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian FT (200 MHz) spectrometer with TMS as the internal standard. ^{13}C NMR spectra were recorded on INOVA (500 MHz) spectrometer. IR spectra were recorded on a Perkin-Elmer Model 283B and Nicolet 740 FT-IR instruments. Mass spectra were recorded on a VG Micromass 7070H instrument.

3.2. Starting materials

The 3-cyano-4-trifluoromethyl-6-substituted 2(1H) pyridones (**6**) were prepared by the known method [6]. All the other reagents were obtained from commercial sources.

3.3. Preparation of 3-cyano-1-methyl-4-trifluoromethyl-6-substituted 2(1H) pyridones (*5a* and *b*)

1,1,1-Trifluoro-2,4-pentanedione or 4,4,4-trifluoromethyl-1-phenyl-1,3-butanedione **4** (7.7 mmol) was dissolved in ethanol (10 ml) and *N*-methyl cyanoacetamide (8.1 mmol) piperidine (0.2 ml) was added. The reaction mixture was heated to reflux for 3 h, while stirring, then the reaction mass was allowed to reach the room temperature and the solid which separated was filtered, washed with cold ethanol and dried.

3.3.1. 3-Cyano-N-1,6-dimethyl-4-trifluoromethyl 2(1H)-pyridone (*5a*)

Melting point 166 °C, IR (KBr): 2200, 1650, 1275, 1175 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.6 (s, 3H, CH_3); 3.65 (s, 3H, N–CH_3); 6.35 (s, 1H, C_5–H). MS: *m/z* 216 (M^+, base peak), 187, 161, 119, 69.

3.3.2. 3-Cyano-N-methyl-6-phenyl-4-trifluoromethyl-2(1H) pyridone (*5b*)

Melting point 128 °C, IR (KBr): 2200, 1650, 1210, 1130 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.5 (s, 3H, N–CH_3), 6.4 (s, 1H, C_5–H), 7.4 (m, 2H, Ar–H), 7.58 (m, 3H, Ar–H). MS: *m/z* 278 (M^+, base peak), 250, 182, 69.

3.4. General procedure for preparation of N-acetyl-3-cyano-4-trifluoromethyl-6-substituted 2-pyridones (*7*)

3-Cyano-4-trifluoromethyl-6-substituted 2(1H) pyridones **6** (8.0 mmol) were taken in excess acetic anhydride (12 ml) and glacial acetic acid (2 ml) was added. The reaction mixture was heated to become homogenous at 110 °C and further continued for 4 h at 140 °C bath temperature while stirring. Then the reaction mixture was allowed to come to room temperature and transferred onto crushed ice. The separated solid was collected on Buchner funnel, dried and purified by column chromatography over silica gel (60–120 mesh) using chloroform as eluent to give products **7**.

3.4.1. N-acetyl-3-cyano-6-phenyl-4-trifluoromethyl-2-pyridone (*7a*)

Melting point 101 °C, IR (KBr): 3086, 2230, 1790, 1650, 1360, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.52 (s, 3H, CH_3); 7.53 (m, 3H, ArH); 8.00 (s, 1H, C_5–H); 8.07 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ: 166.9, 161.1, 159.5, 143.6 (q, $J = 25$ Hz), 134.6, 131.6, 128.8, 127.7, 120.0 (q, $J = 275$ Hz), 114.3, 110.7, 20.2. MS: *m/z* 306 (M^+), 264 (base peak), 236, 216. Analysis: Calc. for $C_{15}H_9F_3N_2O_2$: C, 58.83; H, 2.96; N, 9.14%. Found: C, 58.91; H, 2.92; N, 9.22%.

3.4.2. N-acetyl-3-cyano-6-(4-methyl phenyl)-4-trifluoromethyl-2-pyridone (*7b*)

Melting point 131 °C, IR (KBr): 2250, 1780, 1650, 1275, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.40 (s, 3H, CH_3); 2.51 (s, 3H,–CH_3); 7.34 (d, 2H, ArH); 7.95 (s, 1H, C_5–H); 8.00 (d, 2H, ArH). MS: *m/z* 320 (M^+), 278 (base peak), 250, 69. Analysis: Calc. for $C_{16}H_{11}F_3N_2O_2$: C, 60.00; H, 3.46; N, 8.74%. Found: C, 60.12; H, 3.53; N, 8.72%.

3.4.3. N-acetyl-3-cyano-6-(4-chlorophenyl)-4-trifluoromethyl-2-pyridone (*7c*)

Melting point 141 °C, IR (KBr): 2200, 1790, 1650, 1250, 1175 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.5 (s, 3H, CH_3); 7.5 (d, 2H, ArH); 7.95 (s, 1H, C_5–H); 8.02 (d, 2H, ArH). MS: *m/z* 340 (M^+), 298, 271, 69. Analysis: Calc. for $C_{15}H_{18}ClF_3N_2O_2$: C, 52.88; H, 2.36; N, 8.22%. Found: C, 52.95; H, 2.42; N, 8.31%.

3.4.4. N-acetyl-3-cyano-6-methyl-4-trifluoromethyl-2-pyridone (*7d*)

Melting point 112 °C, IR (KBr): 2200, 1775, 1650, 1225 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3); 2.53 (s, 3H, –CO–CH_3); 6.35 (s, 1H, C_5–H). MS: *m/z* 244 (M^+), 202 (base peak), 174, 69. Analysis: Calc. for $C_{10}H_7F_3N_2O_2$: C, 49.19; H, 2.88; N, 11.47%. Found: C, 49.24; H, 2.82; N, 11.54%.

3.5. General procedure for preparation of N[E,Z-1′,2′-bis(methoxycarbonyl) ethenyl]-3-cyano-4-trifluoromethyl-6-substituted-2-pyridones (*8a-d*)

The *N*-acetyl-3-cyano-4-trifluoromethyl-6-substituted-2(1H) pyridones (7) (1.8 mmol) were dissolved in chloroform and DMAD (1.9 mmol) was added to it. Then, the homogenous reaction mixture coated on to neutral alumina and exposed to the microwave irradiation and the reaction

was followed by TLC. After completion of reaction, the resulted mass directly taken on to the column of silica gel (100–200 mesh), eluted with chloroform and ethyl acetate (9:1) and separated the *E*, *Z* isomers of compound (**8**).

*3.5.1. N[E,Z-1′,2′-bis(methoxycarbonyl)ethenyl]-3-cyano-4-trifluoromethyl-6-phenyl-2-pyridone (**8a**'E', 'Z') (reaction time 5 min)*

3.5.1.1. 'E' isomer. Melting point 136 °C, IR (KBr): 2225, 1750, 1725, 1675, 1550, 1275 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.70 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 6.51 (s, 1H, C_5–H); 6.92 (s, 1H, vinyl–H); 7.29–7.50 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 160.30, 160.20, 159.00, 156.10, 147.00, 137.50, 132.50, 131.50, 129.00, 128.00, 120.00 (q, $J = 250$ Hz), 111.50, 103.75, 54.00, 53.00. MS: *m/z* 406 (M^+), 387, 375, 347 (base peak), 315, 267, 259, 149, 102. Analysis: Calc. for $C_{19}H_{13}F_3N_2O_5$: C, 56.16; H, 3.22; N, 6.89%. Found: C, 56.28; H, 3.36; N, 6.95%.

3.5.1.2. 'Z' isomer. Melting point 115 °C, IR (KBr): 2250, 1750, 1725, 1675, 1275 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.71 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 6.00 (s, 1H, vinyl–H); 6.56 (s, 1H, C_5–H); 7.24 (m, 2H, ArH); 7.34 (m, 3H, ArH). MS: *m/z* 406 (M^+), 376, 348 (base peak), 316, 280, 260, 212,168,150, 114. Analysis: Calc. for $C_{19}H_{13}F_3N_2O_5$: C, 56.16; H, 3.22; N, 6.89%. Found: C, 56.22; H, 3.28; N, 6.82%.

*3.5.2. N[E,Z-1′,2′-bis(methoxycarbonyl)ethenyl]-3-cyano-4-trifluoromethyl-6-(4-methylphenyl)-2-pyridone (**8b**'E', 'Z') (reaction time 5 min)*

3.5.2.1. 'E' isomer. Melting point 126 °C, IR (KBr): 2250, 1750, 1725, 1650, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.41 (s, 3H, CH_3); 3.74 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 6.45 (s, 1H, C_5–H); 6.96 (s, 1H, vinyl–H); 7.25 (d, 2H, ArH); 7.34 (d, 2H, ArH). MS: *m/z* 420 (M^+), 389, 361, 329, 291 (base peak), 132, 91, 69. Analysis: Calc. for $C_{20}H_{15}F_3N_2O_5$: C, 57.14; H, 3.59; N, 6.66%. Found: C, 57.27; H, 3.53; N, 6.72%.

3.5.2.2. 'Z' isomer. Melting point 88 °C, IR (KBr): 2250, 1750, 1725, 1675, 1275 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.4 (s, 3H, CH_3); 3.71 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 5.95 (s, 1H, vinyl–H); 6.48 (s, 1H, C_5–H); 7.24 (d, 2H, ArH); 7.28 (d, 2H, ArH). MS: *m/z* 420 (M^+), 389, 361, 291 (base peak), 132, 91, 69. Analysis: Calc. for $C_{20}H_{15}F_3N_2O_5$: C, 57.14; H, 3.59; N, 6.66%. Found: C, 57.18; H, 3.62; N, 6.74%.

*3.5.3. N[E,Z-1′,2′-Bis(methoxycarbonyl) ethenyl]-3-cyano-4-trifluoromethyl-6-(4-chlorophenyl)-2-pyridone (**8c**'E', 'Z'): (reaction time 5 min)*

3.5.3.1. 'E' isomer. Melting point 129 °C, IR (KBr): 2200, 1760, 1725, 1680, 1250, 1175 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.71 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 6.42 (s, 1H, C_5–H); 6.91 (s, 1H, vinyl–H); 7.28 (d, 2H, ArH); 7.37 (d, 2H, ArH). MS: *m/z* 440 (M^+), 381 (base peak), 349, 311, 83. Analysis: Calc. for $C_{19}H_{12}ClF_3N_2O_5$: C, 51.77; H, 2.74; N, 6.35%. Found: C, 51.84; H, 2.78; N, 6.42%.

3.5.3.2. 'Z' isomer. Melting point 105 °C, IR (KBr): 2225, 1750, 1730, 1650, 1275 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.68 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 5.96 (s, 1H, vinyl–H); 6.47 (s, 1H, C_5–H); 7.37–7.47 (m, 4H, ArH). MS: *m/z* 440 (M^+), 381 (base peak), 349, 311, 258, 111. Analysis: Calc. for $C_{19}H_{12}ClF_3N_2O_5$: C, 51.77; H, 2.74; N, 6.35%. Found: C, 51.88; H, 2.71; N, 6.47%.

*3.5.4. N[E,Z-1′,2′-bis(methoxycarbonyl)ethenyl]-3-cyano-4-trifluoromethyl-6-methyl-2-pyridone (**8d**'E', 'Z'): (reaction time 4 min)*

3.5.4.1. 'E' isomer. Melting point 136 °C, IR (KBr): 2250, 1740, 1725, 1675, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.3 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 6.4 (s, 1H, C_5–H); 7.3 (s, 1H, vinyl–H). MS: *m/z* 344 (M^+), 313, 285 (base peak), 253, 69. Analysis: Calc. for $C_{14}H_{11}F_3N_2O_5$: C, 48.84; H, 3.22; N, 8.13%. Found: C, 48.97; H, 3.24; N, 8.18%.

3.5.4.2. 'Z' isomer. Melting point 121 °C, IR (KBr): 2230, 1750, 1725, 1660, 1275, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.31 (s, 3H, CH_3); 3.76 (s, 3H, OCH_3); 3.9 (s, 3H, OCH_3); 6.21 (s, 1H, vinyl–H); 6.42 (s, 1H, C_5–H). MS: *m/z* 344 (M^+), 325, 313, 285 (base peak), 111, 69. Analysis: Calc. for $C_{14}H_{11}F_3N_2O_5$: C, 48.84; H, 3.22; N, 8.13%. Found: C, 48.88; H, 3.31; N, 8.24%.

Acknowledgements

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