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## A FACILE TRANSFER OF DICYANO METHYLENE GROUP BETWEEN ARYLIDENEMALONONITRILE AND ALDEHYDE

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Abstract : Arylidenemalononitrile undergoes facile exchange of dicyano methylene group with  $\beta$ -formyl steroidal enamide as well as aromatic aldehydes under mild base catalysed reaction.

The transfer reactions have attracted considerable attention as valuable tool in synthetic organic chemistry<sup>1</sup>. Nonetheless, the salient feature of these transformations is primarily the mild reaction condition which enable them to be more advantageous in transhydrogenation<sup>2</sup>, transalkylation<sup>3</sup>, transacetylation<sup>4</sup>, transesterification<sup>5</sup>, transamidation<sup>6</sup>, transamination<sup>7</sup> and transetherification<sup>8</sup>. The arylidenemalononitrile derivatives are important synthones<sup>9</sup> and have received renewed interests<sup>10</sup>. Recently, research efforts in our laboratory directed towards manipulation of steroidal-D ring necessitated the exploration of newer methods<sup>11</sup>. We were attracted by the scope of a newer class of  $\beta$ -formyl steroidal-17enamide<sup>12</sup> as a potential substrate in the emerging field of enamide<sup>13,14</sup>. Although many synthetic methods for preparation of arylidenemalononitrile utilizing Knovenagel condensation have been reported<sup>9a-b,15</sup>, but in general these methods have limitations of harsh reaction conditions which are unfavorable for substrates possessing alkali sensitive O- or N-protecting functional groups. Herein, we report our findings on a base catalysed transfer reaction of dicyano methylene

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functional group between arylidenemalononitrile and aldehydes under mild conditions.



16-Formyl-17-steroidal enamides (1a-b) were obtained from 16-DPA oxime by treatment with Vilsmeier reagent in excellent yields<sup>12</sup>. Treatment of 1a with arylidenemalononitrile (2a, X=H, Y=CN) in ethanol under the influence of pyrrolidine led to the transfer of dicyano methylene group affording 17-acetamido-steroidal-16-formylidene malono nitrile(4a) in 95% yield. Similarly, reaction of 1a with arylidenecyanoacetate(3a, X=H, Y=COOEt) afforded the product 5a in quantitative yield. In order to investigate the influence of the  $\beta$ -enamido group on exchange reaction, compound 1a was subsequently reacted with 2b-d (X=Cl<Me<NMe<sub>2</sub>). It was observed that the yield of the product 4a decreases with increasing electron releasing capacity of the para substituents of aldehydes. In case of 2d (X=NMe<sub>2</sub>), no transfer reaction with 1a was observed at

Aldehyde	Ylidenemalono-	Product <sup>a</sup>	Yield <sup>b</sup> (%)	Reaction time
	nitrile			hr
1a	2a	4a	95	3
1a	2b	4a	80	3
1a	2c	<b>4</b> a	60	3
1a	2d	-	-	12
6a	2b	2a	15	6
6a	2c	-	-	12
6a	4a	-	-	12
6a	2d	-	-	12
6b	2a	2b	45	6
6b	2c	-	-	12
6b	4a	-	-	12
6b	2d	-	-	12
6c	2a	2c	75	3
6c	2b	2c	60	3
6c	<b>4</b> a	-	-	12
60	2d	-	-	12
6d	2a	2d	98	3
6d	2b	2d	85	3
6d	2c	2d	80	3
6d	<b>4</b> a	2d	75	3

Table-I. Yields of transfer reaction products between aldehydes and arylidinemalononitriles

<sup>a</sup> All reactions were carried at room temperature; <sup>b</sup> Isolated yields after colomn chromatography.

all. Similarly compound **1b** reacted with **2a-c** and **3a-c** to afford **4b** and **5b** in 58-97% yields. Interestingly, the base labile 3-acetoxy or 17-acetamido groups of **1a** were intact under the reaction condition. However, our earlier attempt on Knoevenagel condensation of **1a** with malononitrile required<sup>12</sup> either strong alkaline condition (KOH/MeOH) or thermal condition conceding hydrolysis of the protecting group.

In an effort to develop a more general method for transfer of dicyano methylene functional group, we carried an independent investigation between p-arylaldehydes (**6a-d**) and ylidenemalononitriles (**2a-d**)(table-I). Benzaldehyde **6a** 

(Z=H) failed completely to exchange with 2c-d (X=Me, NMe<sub>2</sub>), although it reacted with 2b to afford exchange product 2a in poor yield (15%). On the other hand, the electron rich aldehyde 6d (Z= NMe<sub>2</sub>) conveniently exchanged with 2a-caffording 2d in excellent yields (80-98%). Similarly aldehydes 6a-c did not react with 4a, however 6d successfully participated in transfer reaction to afford 2d in 75% yield.

The reaction is believed to undergo through an unstable tetracyclic intermediate  $[\mathbf{A}]^{16}$  resulted from the nucleophilic attack of the base induced



benzylidenemalononitrile(2a) onto 16-formyl group of 1a. Rearrangement and bond cleavage of the intermediate would result 4a with loss of benzaldehyde (6a) which was isolated and identified through spectroscopy.

In summary, we have demonstrated a simple dicyano methylene transfer reaction of arylidenemalononitrile with aldehydes under mild base catalysis. Overall methodology provides a fairly general and attractive approach to formylidene malononitriles bearing base sensitive protecting groups. Efforts to clarify reaction mechanism, broaden scope and develop synthetic application<sup>17</sup> of these reactions are under progress.

#### **Experimental** :

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded by using a Perkin Elmer 237 and 580B spectrometers in KBr discs. <sup>1</sup>HNMR spectra were recorded in Varian T-60 and Bruker 300 MHz spectrometer. Mass spectra were recorded on a Incos 50 mass spectra machine. Elemental analysis were obtained from a Perkin Elmer Series II 2400 machine. Commercial grade 16-DPA was employed as starting material for synthesis.

# General Procedure for transfer reaction between arylidenemalono nitrile and aldehyde :

To a solution of 3B-acetoxy-17-acetamido-16-formyl-androst-5,16-diene (1a, 399mg, 0.001 mol) in dry ethanol (40 ml) was added benzylidene malononitrile (2a, 308 mg, 0.002 mol) and the solution was stirred at room temperature in presence of a catalytic amount of pyrrolidene for 3h.. On completion of the reaction, it was worked up by poring into ice cold water (500 ml) and carefully neutralized with dilute hydrochloric acid and stirred for 0.5h when a yellow solid product separated out. The product was filtered, washed with water and dried over anhydrous P2O5 in a desicator under reduced pressure. Recrystallisation from hexane-diethyl ether (8:2) afforded 3B-Acetoxy-17acetamido-androst-5,16-dieno-16-formylidenemalononitrile(4a) as light yellow crystals, yield 425mg (95%), mp 201°C, Rf = 0.1 in toluene/acetone(95:5), IR (KBr) v<sub>max</sub> 3280, 2910, 2230, 1710, 1650, 1585, 1270 cm<sup>-1</sup>; <sup>1</sup>HNMR (d<sub>6</sub>-DMSO)  $\delta$  9.31(bs, 1H, exchangeable with D<sub>2</sub>O), 7.79(s, 1H), 5.23 (bs, 1H), 4.45 (m, 1H), 2.10(s, 3H), 1.89(s, 3H), 1.00(s, 3H), 0.98(s, 3H), 2.30-1.55(m, 17H); mass spectrum (EI) m/z 387(M<sup>+</sup>-CH<sub>3</sub>COOH), 372[(M<sup>+</sup>- CH<sub>3</sub>COOH)-15], 345[(M<sup>+</sup>-CH<sub>3</sub>COOH)-42(CH<sub>2</sub>=C=O)], 330[{(M<sup>+</sup>- CH<sub>3</sub>COOH)-42}-15], 237, 121; Anal. Calcd. For C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub> : C, 72.45; H, 7.49; N, 9.39. Found : C, 71.98; H, 7.60; N, 8.79. 3B-Benzoyloxy-17-acetamido-androst-5,16-dieno-16-formylidene malono nitrile(4b), yellow crystals, yield 458 (90%), mp 230°C, Rf=0.1 in Toluene:acetone(95:5), IR (KBr) v<sub>max</sub> 3275, 2920, 2225, 1715, 1650, 1585, 1270 cm<sup>-1</sup>; <sup>1</sup>HNMR (d<sub>6</sub>-DMSO)  $\delta$  9.40(bs, 1H, exchangeable with D<sub>2</sub>O), 7.85(s, 1H), 7.75-7.20(m, 5H), 5.30 (bs, 1H), 4.50 (m, 1H), 1.95(s, 3H), 1.00(s, 3H), 0.95(s, 3H), 2.30-1.55(m, 17H); mass spectrum (EI) m/z 387(M<sup>+</sup>-PhCOOH), 372[(M<sup>+</sup>-PhCOOH)-15], 345[(M<sup>+</sup>- PhCOOH)-42]; Anal. Calcd. For C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub> : C, 75.39; H, 6.92; N, 8.28. Found : C, 75.12; H, 9.78; N, 8.05.

3β-Acetoxy-17-acetamido-androst-5,16-dieno-16-formylidenecyanoacetate (5a), thin yellow flakes, yield 464mg(94%), mp 180°C, TLC in CHCl<sub>3</sub>:MeOH (98:2), Rf = 0.20, IR(KBr)  $\nu_{max}$  3250, 2910, 2240, 1700, 1525, 1230, 1035 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 8.18(bs,1H, exchangeable with D<sub>2</sub>O), 7.80(s, 1H), 5.20(bs, 1H), 4.40(m, 1H), 4.15(q, 2H), 2.20(s, 3H), 1.95(s, 3H), 1.25(t, 3H), 1.00(s, 3H), 0.98(s, 3H), 2.25-1.05(m, 17H); mass spectrum (EI) m/z 494(M<sup>+</sup>), 434(M<sup>+</sup>-CH<sub>3</sub>COOH), 392[(M<sup>+</sup>- CH<sub>3</sub>COOH)-42]; Anal. Calcd. For C<sub>29</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub> : C, 70.45; H, 7.69; N, 5.66. Found : C, 69.83; H, 7.63; N, 5.54. 3β-Benzoyloxy-17acetamido-androst-5,16-dieno-16-formylidenecyanoacetate(**5b**), yellow flakes, yield 511mg(92%), mp 205°C, Rf = 0.20 in CHCl<sub>3</sub>:MeOH (98:2), IR(KBr)  $\nu_{max}$ 3260, 2900, 2245, 1705, 1520, 1220, 1040 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 8.25(bs,1H, exchangeable with D<sub>2</sub>O), 7.80(s, 1H), 7.70-7.15(m, 5H), 5.25(bs, 1H), 4.40(m, 1H), 4.20(q, 2H), 1.90(s, 3H), 1.20(t, 3H), 1.05(s, 3H), 0.95(s, 3H), 2.20-1.05(m, 17H); mass spectrum (EI) m/z 434(M<sup>+</sup>- PhCOOH), 392 ; Anal. Calcd. For C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub> : C, 73.36; H, 7.24; N, 5.03. Found : C, 73.50; H, 753; N, 4.95.

p-Chlorobenzylidenemalononitrile(**2b**), yield 85mg(45%), mp 161°C (litt<sup>18</sup>162-63°C), Rf = 0.65 in Hexane:Ethylacetate(90:10); IR(KBr)  $v_{max}$  2950, 2210, 1560, 1450, 800 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$  7.50(d,2H, J=8Hz), 7.40(s, 1H), 7.10(d, 2H, J=8Hz), 2.30(s, 3H); mass spectrum (EI) m/z 138(M<sup>+</sup>). Tolylidenemalononitrile(**2c**), yield 126mg(75%), mp 134°C (litt<sup>19</sup>134°C), Rf = 0.60 in Hexane:Ethylacetate(95:5); IR(KBr)  $v_{max}$  2930, 2220, 1580, 1450, 810 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$  7.50(d,2H, J=8Hz), 7.30(s, 1H), 7.00(d, 2H, J=8Hz), 2.30(s, 3H); mass spectrum (EI) m/z 168(M<sup>+</sup>). P-(NN-Dimethylamino)benzylidene malononitrile(**2d**), yield 193mg(98%), mp 175°C (litt<sup>19</sup>178°C), Rf = 0.25 in Hexane:Ethylacetate(90:10); IR(KBr)  $v_{max}$  2960, 2215, 1550, 1480cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$  7.55(d,2H, J=9Hz), 7.50(s, 1H), 7.15(d, 2H, J=9Hz), 3.05(s, 3H); 2.4(s, 3H); mass spectrum (EI) m/z 197(M<sup>+</sup>).

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