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STUDIES ON $S_{RN}1$ REACTIONS. PART 8[1]

NEW AND DIRECT ARYLATION AND HETARYLATION OF β-DICARBONYL COMPOUNDS BY $S_{RN}1$

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Abstract—Arylation of β-dicarbonyl compounds is carried out by photostimulated $S_{RN}1$ reaction between bromobenzonitriles or bromocyanopyridine and β-dicarbonyl derived monoanions.

The $S_{RN}1$ reaction which happens to be one of the most efficient reactions available for arylation of monoketones[2] was until now reported not to occur between aryl halides and monoanions of β-dicarbonyl compounds.[3,4] Even 2-chloroquinoline, a very reactive substrate, failed to react with these anions.[4]

However, 1,3-dianions of β-diketones are suitable nucleophiles and react quite well through the terminal carbanion site[3,5] (Scheme 1).

Our interest in the extension of the $S_{RN}1$ reaction led us to discover new synthetic methods for heterocyclic compounds (indoles, aza indoles, benzofurans, isocarbostyrils, isoquinolines) **6** based upon the results of investigations of the effects of various functionalities (NH_2, OCH_3, $CONH_2$, CH_2NH_2) borne by the aryl substrate.

We report now that the cyano electron withdrawing group allow high yield $S_{RN}1$ reaction to occur with β-dicarbonyl derived monoanions.

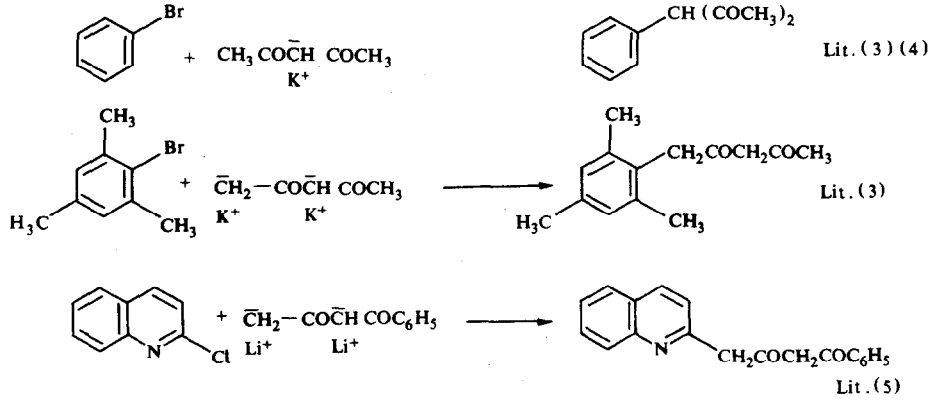
RESULTS

The reaction between 2-bromobenzonitrile **1** and the monanion derived from secondary (**a**) and tertiary (**b**) malonates or from ethyl-cyanoacetate (**c**) gives the expected arylated derivatives **2**, **3** or **4** in excellent yields (Table 1). The products of the reaction carried out with β-diketone or ethyl acetoacetate derived monoanions (**d–g**) are very sensitive to the work up conditions. Only when the reaction mixture is poured onto ice cooled concentrated hydrochloric acid (conditions A, Table 1) are the expected substitution products **5** or **7** obtained. Otherwise, after basic work up (conditions B, Table 1) a retro-Claisen fragmentation (loss of $COCH_3$ or $COCH_2CO_2Et$) occurs and compounds **6**, **8** or **9** are obtained. A cyclic β-diketone such as dimedone (**h**) gives, nevertheless, the expected derivative **10** without retro-Claisen elimination.

The *m*-bromo **11** and *p*-bromo benzonitrile **14** also undergo $S_{RN}1$ reaction when reacted with β-dicarbonyl monoanions, but **14** reacts more smoothly than **1** and **11**. The anticipated derivatives **12** and **13**, **15** and **17** are obtained respectively from **11** or **14** treated with (**d**) or (**e**) (acidic work up condition A, Table 1) whilst the loss of $COCH_3$ also occurs under condition B (reaction of **14** with **e**) as observed with the *ortho*-bromo-benzonitrile **1**. The 2-bromo-3-cyanopyridine **18** reacts with the monoanions (**a**), (**b**) or (**c**) faster than the bromobenzonitriles (Table 2), and gives excellent yields of the heteroarylated derivatives **19**, **20** and **21**. It was not possible to avoid the elimination of the acyl group in reactions with the monoanions (**d**), (**e**), (**g**), even under acidic conditions work up. Similar fragmentations were reported in the synthesis of analogous derivatives.[7,11]

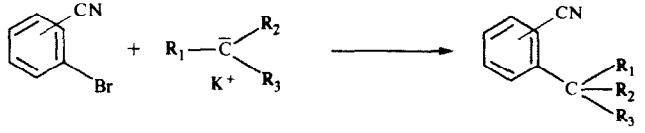
DISCUSSION

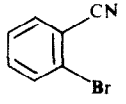
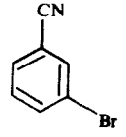
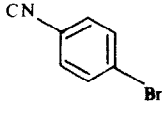
These reactions show features characteristic of a $S_{RN}1$ mechanism (Scheme 2) since we have observed that (i) withoug photostimulation, the substrate **1** was recovered unchanged when treated with monoanions (**a**) or (**b**); (ii) the addition of a radical scavenger (galvinoxyle 10%)



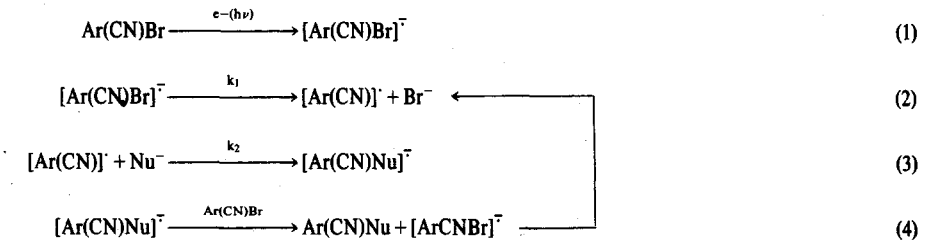
Scheme 1

Table 1.



Substrate	Nucleophile*	Reaction time/h	Work up conditions†	Product yield (%)‡		
 **1**	**(a)** R_1=H; R_2=R_3=COOEt	6	B or A	**2** R_1=H; R_2=R_3=COOEt	78	(100)
	(b) R_1=C_2H_5; R_2=R_3=COOEt	2	B	**3** R_1=C_2H_5; R_2=R_3=COOEt	80	(100)
	(c) R_1=H; R_2=COOEt; R_3=CN	2	B	**4** R_1=H; R_2=COOEt; R_3=CN	90	(100)
	(d) R_1=H; R_2=R_3=$COCH_3$	1	A	**5** R_1=H; R_2=R_3=$COCH_3$ §	90	(100)
		3	B	**6** R_1=R_3=H; R_2=$COCH_3$	68	
	(e) R_1=H; R_2=COOEt; R_3=$COCH_3$	1	A	**7** R_1=H; R_2=COOEt; R_3=$COCH_3$ §	80	(100)
			B	**8** R_1=R_3=H; R_2=COOEt	90	(100)
	(f) R_1=H; R_2=COOEt; R_3=$COCH_2COOEt$	2	B	**8** –id–	90	(100)
	(g) R_1=CH_3; R_2=COOEt; R_3=$COCH_3$	2	B	**9** R_1=CH_3; R_2=H; R_3=COOEt	60	
	(h) R_1=H; R_2–R_3=$COCH_2-C(CH_3)-CH_2CO-$	1	B	**10** R_1=H; R_2–R_3=$COCH_2-C(CH_3)-CH_2-CO$ §	80	
 **11**	**(d)**	1	A	**12** R_1=H; R_2=R_3=$COCH_3$	90	(100)
	(e)	1	A	**13** R_1=H; R_2=COOEt; R_3=$COCH_3$	80	(100)
 **14**	**(d)**	7	A	**15** R_1=H; R_2=R_3=$COCH_3$	63	
	(e)	4	B	**16** R_1=R_3=H; R_2=COOEt	70	
	(e)	4	A	**17** R_1=H; R_2=COOEt; R_3=$COCH_3$	70	

*The β-dicarbonyl compound and *t*-ButOK in fourfold molar excess over the substrate.
†B = Basic conditions work up; A = Acidic conditions work up.
‡% of isolated product (NMR or CPG yield estimation).
§Under enol form.



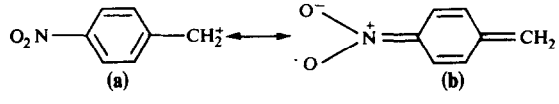
Ar(CN)Be = **1**, **11**, **14**, **18**; Nu^- anions (**a–h**)

Scheme 2.

brought about a significant delay compared with a blank reaction (photostimulated reaction between **1** and (**a**)). These two experimental facts supporting the $S_{RN}1$ mechanism are understood by the lack of chain initiation in the dark (eqn 1) and by the scavenging of the radical [ArCN]· (eqn 2) which prevents the chain propagation untill all the galvinoxyl has been consumed.

The reason why the substrates **1**, **11**, **14** and **18** react with β-diketone monoanions while bromobenzene, bromopyridine, chloroquinoline and 2-bromo-benzamide do not, is closely related to the presence of the cyano group and to its strong withdrawing effect. The reaction occurs whatever the position of C≡N relative to the leaving group, but is slower with *p*-bromobenzonitrile. These facts indicate that C≡N exerts not anchimeric but electronic effects (–I–E) which could influence one or several steps of the $S_{RN}1$ radical chain mechanism depicted on Scheme 2.

†The argument put forward by the authors is based upon the reactivity of the 2-quinolyl radical (Qn·) compared with that of the *p*-nitrobenzyl radical (**a**) toward the diethyl malonate anion. N. Kornblum *et al.* have recently pointed out (*J. Org. Chem.* **45**, 5294 (1980)) that the canonical form (**b**) has also to be considered and that (eqn 3) in this case could be represented as a Michael attachment of nucleophile to an unsaturated system. This possibility is of course unavailable for the aryl radical (Q_n·).



(a) (b)

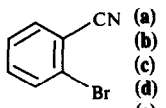
The first two steps (eqn 1, 2) do not appear to be determinant for the failure of halogenobenzene to react with β-dicarbonyl monoanions as evidenced by the following. The aryl radical anion $[C_6H_5]^-$ generated from iodobenzene with a small amount of acetone enolate in the presence of a large excess of the monoanion **b** (eqn 1) extrudes I^- in a fast intramolecular process which gives $[C_6H_5]$· (eqn 2). No substituted final product $C_6H_5C(C_2H_5)(COOEt)_2$ resulting from the attack of $C_6H_5^-$ onto the monoanion (**b**) in excess was found.

According to Wolfe *et al.*[5] the bimolecular process described by (eqn 3) is not crucial for explaining the failure of the 2-quinolyl radical (Qn·) to react with the malonate.† However the cyano-phenyl radical (ArCN·) is expected to be more electrophilic than (Qn·) toward the same nucleophile ($k_2[ArCN^·] > k_2[Qn^·]$) and at first sight the reason explaining both the failure of (Ar·) or (Qn·) to react with the malonate and the ready reaction of Ar(CN)· might be found in (eqn 3).

The explanation of the easy $S_{RN}1$ reactivity of cyanobromoaryl substrates would lie also in the fact that the second radical anion $[Ar(CN)CH(COR)_2]^-$ is easily oxidized by the substrate Ar(CN)X. In a single step (eqn 4) the final substitution product $Ar(CN)CH(COR)_2$ is formed and the first radical anion $[Ar(CN)X]^-$ is regenerated.

Radical anions $[ArNu]^-$ (Ar = C_6H_5 or 2-Qn)· are not oxidized by the corresponding substrates ArX (which have lower electron affinity than Ar(CN)X (**1**, **11**, **14**, **18**) and the chain propagation can therefore not take place. It is of note that Ar(CN)X is itself more easily reduced by

Table 2.

Substrate	Nucleophile*	Reaction time	Work up conditions†	Product yield (%)‡		
	(**a**) R_1=H; R_2=R_3=COOEt	3 h	B	**19** R_1=H; R_2=R_3=COOEt	90	(100)
	(**b**) R_1=C_2H_5; R_2=R_3=COOEt	10 mn	B	**20** R_1=C_2H_5; R_2=R_3=COOEt	92	(100)
	(**c**) R_1=H; R_2=COOEt; R_3=CN	1 h	B	**21** R_1=H; R_2=COOEt; R_3=CN	80	(100)
	(**d**) R_1=H; R_2=R_3=$COCH_3$	2 h	B or A	**22** R_1=R_2=H; R_3=$COCH_3$	75	
	(**e**) R_1=H; R_2=COOEt; R_3=$COCH_3$	45 mn	B	**23** R_1=R_2=H; R_3=COOEt	80	(100)
18	(**g**) R_1=CH_3; R_2=COOEt; R_3=$COCH_3$	30 mn	B	**24** R_1=CH_3; R_2=COOEt; R_3=H	82	(100)

*The β-dicarbonyl compound and *t*-But'OK are in four fold molar excess over **18**.
†B = Basic conditions work up; A = Acidic conditions work up.
‡% of isolated product (CPG yield estimation).

Nu^- (eqn 1) than ArX, and that this fact must also come into play for explaining the ready $S_{RN}1$ reactivity of **1**, **11**, **14**, **18**.

Synthetic scope

The introduction of an aryl group onto a β-dicarbonyl compound can be achieved by a variety of methods all of them of limited scope.

The classical method[9] based upon the Ulman reaction[10] was recently reinvestigated[11,12] and its mechanism was shown to require the formation of an intramolecular copper complex between the nucleophile and the carboxylate *ortho* to the leaving group. Very recently, the copper promoted coupling of *ortho* and *para* bromophenols with active methylene compounds (malonate, ethyl acetoacetate, ethyl cyanoacetate) was reported.[13]

Another method available for arylation requires that the leaving group be activated by an *ortho*[14b] or *para*[15] nitro group whereas the introduction of a heteroaryl moiety (2-quinoline or 2-phenanthroline[10] on cyanoacetate or on malonitrile requires no additional activation.[16]

Methods for the introduction of a simple aryl group are based upon the formation of an arynic intermediate[17] or on the use of arylating reagents such as diphenyl iodonium salts,[18] aryl lead triacetate[19] or triphenyl bismuth carbonate.[20]

The method based upon the extended $S_{RN}1$ reaction has several features which makes it advantageous: (i) yields are in most cases high; (ii) the arylation by *o*-, *m*- or *p*- cyano benzene is possible; (iii) tertiary β-dicarbonyl derived anions can also be good nucleophiles; (iv) the monoanions derived from β-diketone (**d**) or from acetic ester (**f**), (**g**) act after acyl elimination as masked $^-CH_2COOR$ nucleophiles. We thus obtained **8**, a homophthalic synthon which we failed to prepare by treating **1** with the lithio-*tert* butyl acetate salt.[21] Here, under mild conditions, with nucleophiles (**e**) or (**f**) which are much easier to handle than the lithio salt, we obtained high yield of the desired product.

CONCLUSION

This first demonstration of the efficient nucleophilic reaction of β-dicarbonyl derived monoanions on properly functionalised aromatic substrates considerably enlarges the scope of the $S_{RN}1$ reaction.

EXPERIMENTAL

M.p. were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrometer. NMR spectra, ($CDCl_3$) internal standard: $Si(CH_3)_4$, were recorded on a Varian T60 or a Perkin–Elmer R13 instrument. Low resolution mass spectra were obtained with an AEI MS9 spectrograph; high resolution mass determination were carried out by the mass spectrometry service of our Institute. Purification was achieved either by column chromatography (alumina or silica gel) or by preparative thin layer plates (Kiesegel 60 GF 254 Merck); elution dichloromethane/methanol in various proportions.

General procedure for $S_{RN}1$ reactions

Dry ammonia (50 ml) was condensed under argon atmosphere in a three neck flask (100 ml) or in a two neck tube (100 ml, 3 cm diameter) fitted with a dry ice condenser and rubber taps. Freshly sublimed potassium *t*-butoxide (4 mmole, 448 mg), the active methylene compound (4 mmole) and then the substrate (ArXY, 1 mmole) were added. The flask is then introduced in a Rayonet apparatus (RPR 204 from the S.O. New England Ultraviolet Co.) equipped with 4 tubes RVL 3.000 and a magnetic stirrer. The reaction was monitored by taking out aliquots, which after proper work up were examined by thin layer chromatography. The end of the reaction was indicated by the consumption of the substrate.

(a) *Acidic conditions work up.* The liquid ammonia solution is poured on iced 6*N* hydrochloric acid solution (300 ml), cooled in an ice bath, in a well ventilated hood. Extraction is then carried out with methylene chloride (3 × 50 ml). The organic phase is washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, leaving the crude product.

(b) *Basic conditions work up.* Ammonium chloride is added and the ammonia is evaporated in a well ventilated hood, leaving the crude reaction product which is dissolved in methylene chloride. The organic phase is washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

[o-*Cyano-phenyl*] *malonic acid diethyl ester* **2**. The reaction between the *o*-bromo cyano benzene **1** and the monoanion (**a**) derived from the malonic acid diethyl ester (irradiation time 6 h), after alkaline work up conditions yielded **2**: oil (203 mg, 78%). IR: 2975, 2210, 1730, 1360, 1300 cm^{-1}; MS *m/e* 261.1004 (M^+) $C_{14}H_{15}NO_4$ requires 261.1001; 216; 189; 161; H^1NMR: 1.26 (t, 6H), 4.26 (q, 4H), 5.07 (s, 1H), 7.40–7.80 (m, 4H).

2-*Ethyl*-2-[o-*cyano phenyl*] *malonic acid diethyl ester* **3**. The reaction between **1** and the monoanion (**b**) derived from the ethyl malonic acid diethyl ester (irradiation time 2 h, flask) after work up conditions [B] yielded **3**: oil (213 mg, 80%). IR: 2975, 2210, 1720, 1360, 1300 cm^{-1}, MS *m/e* 289.1274 (M^+) $C_{16}H_{19}NO_4$ requires 289.1314; H^1NMR 0.91 (t, 3H), 1.29 (t, 6H), 2.53 (q, 2H), 4.33 (q, 4H), 7.3–7.7 (m, 4H).

[o-*Cyano phenyl*] *cyano acetic acid ethyl ester.* **4**. The reaction between **1** and the monoanion (**c**) derived from cyano acetic ethyl ester followed by work up [B] yields **4**: m.p. 69° (167 mg, 78%). IR: 2980, 2210, 1735, 1360, 1220 cm^{-1}; MS (electron impact): no M^+ (chemical ionization (CH_4)) *m/e* 215 ($M^+ + 1$). High resolution measured on $M^+ - 45$ (OC_2H_5) 169.0402. $C_{10}H_5N_2O$ requires 169.0402; H^1NMR 1.3 (t, 3H), 4.25 (q, 1H), 5.15 (s, 1H), 7.5–7.9 (m, 4H).

3-[o-*Cyano phenyl*] 2,4-*pentanedione* **5**. The reaction between **1** and the monoanion (**d**) derived from the 2,4-pentanedione (irradiation time 1 h (tube) or 3 h (flask)) after work up according to[A] and purification yielded **5** (enol form); m.p. 92–94°; (181 mg, 90%); IR: 3000, 2220, 1600, 1400, 1320 cm^{-1}; MS *m/e* 201.0791 M^+ $C_{12}H_{11}NO_2$ requires 201.0789; 186; 159; H^1NMR 1.90 (s, 6H), 7.3–7.9 (m, 4H).

[o-*Cyano phenyl*] *acetone* **6**. The reaction between **1** and the monoanion (**d**) (reaction time 1 h (tube); 3 h (flask)) after work up under basic conditions [B] and purification afforded **5** m.p. 94° (40 mg, 20%) and **6** oil (108 mg, 68%). IR: 3000, 2220, 1715, 1600, 1410, 1360 cm^{-1}; MS *m/e* 159.06837 (M^+) $C_{10}H_9NO$ requires 159.0684; H^1NMR 2.29 (s, 3H), 3.95 (s, 2H), 7.24–7.78 (m, 4H).

2-[o-*Cyano phenyl*] *acetoacetic acid ethyl ester* **7**. The reaction between **1** and the monoanion (**e**) derived from ethyl acetoacetate followed by work up [A] yielded **7** (enol form): oil, (185 mg, 80%); MS *m/e* 231.0897 (M^+) $C_{13}H_{13}NO_3$ requires 231.0895, 189, 185, 143; H^1 NMR 1.25 (t, 3H), 1.85 (s, 3H), 4.15 (q, 2H), 7.2–7.8 (m, 4H).

[o-*Cyano phenyl*] *acetic acid ethyl ester* **8**. The reaction between **1** and the monoanion (**e**) (irradiation time 1 h (tube), 2 h (flask)) after work up under conditions [B] yielded **8**: m.p. 51° (170 mg, 90%). This same product **8** (90%) was also obtained from the reaction of **1** with the monoanion (**f**), derived from 1,3-acetone dicarboxylic acid diethyl ester (irradiation time 2 h (tube), work up [B]). IR: 3000, 2210, 1720, 1360, 1330 cm^{-1}; MS *m/e* 189.0788 (M^+) $C_{11}H_{11}NO_2$ requires 189.0789; H^1 NMR 1.25 (t, 3H), 3.80 (s, 2H), 4.15 (q, 2H), 7.20–7.70 (m, 4H).

2-[o-*Cyano phenyl*] *propionic acid ethyl ester* **9**. The reaction between **1** and the monoanion (**g**) derived from the 2-methyl acetoacetic ester (irradiation time 4 h (tube)), after basic work up conditions [B] yielded **9**: oil (122 mg, 60%). MS *m/e* 203.0943 (M^+) $C_{12}H_{13}NO_2$ requires 203.0946, 158, 130. IR: 2980, 2210, 1720, 1365, 1220 cm^{-1}; H^1 NMR 1.23 (t, 3H), 1.56 (d, 2H), 4.17 (q, 2H), 4.0 (s, 1H), 7.25–7.8 (m, 4H).

2-[o-*Cyano-phenyl*] 5,5-*dimethyl*-1,3 *cyclohexanedione* **10**. The

reaction between **1** and the monoanion (**h**) derived from dimedone (irradiation time 1 h, (tube)) after basic work up, followed by acidification of the aqueous solution and extraction with methylene chloride yielded **10** (enol form) m.p. 192–195 (192 mg, 80%). IR: 2950, 2210, 1660, 1580, 1370 cm^{-1}. MS: *m/e* 241.1102 (M^+) $C_{15}H_{15}NO_2$ requires 241.1103; H^1 NMR 1.15 (s, 6H), 2.40 (s, 4H), 7.1–7.8 (m, 4H).

3-[m-*Cyano phenyl*] 2,4-*pentanedione* **12**. The reaction between the *m*-bromo cyanobenzene **11** and the monoanion (**d**) (1 h, flask) followed by acidic conditions work up (A) yielded **12** (enol form) m.p. 108°; (179 mg, 89%). Found C, 71.35; H, 5.46; N, 7.12; 0, 15.99%. $C_{12}H_{11}NO_2$ requires C, 71.63; H, 5.51; N, 6.96; O, 15.90. MS *m/e* 201 (M^+), 186, 158; IR: 2975, 2210, 1600, 1400 cm^{-1}; H^1 NMR 1.88 (s, 6H), 7.4–7.9 (m, 4H).

2-[m-*Cyano phenyl*] *aceto acetic ethyl ester* **13**. The reaction between **11** and the monoanion (**e**) (1 h, flask) gave, after acidic work up conditions, the compound **13** oil (180 mg, 80%). Found C, 66.72; H, 5.70; N, 5.98; O, 19.52%. $C_{13}H_{13}NO_3$ requires C, 67.50; H, 5.66; N, 6.06; O, 20.75; MS *m/e* 231 (M^+), 189, 185, 143; IR: 2975, 2210, 1720, 1640, 1600 cm^{-1}; H^1 NMR (enol form): 1.15 (t, 3H), 1.85 (s, 3H), 4.25 (q, 2H), 7.3–7.8 (m, 4H); (keto-ester form): 1.25 (t, 3H), 2.25 (s, 3H), 4.15 (q, 2H), 4.80 (s, 1H), 7.3–7.8 (m, 4H).

3-[p-*Cyano phenyl*]-2,4-*pentanedione* **15**. The reaction between the *p*-bromo cyano benzene **14** and the monoanion (**d**) (7 h, flask) followed by work-up [A] gave **15** (enol form) m.p. 145–150° (subl.) (125 mg, 63%). Found C, 71.58; H, 5.53; N, 7.03; O, 16.10%. $C_{12}H_{11}NO_2$ requires C, 71.63; H, 5.51; N, 6.96; O, 15.90; MS *m/e* 201 (M^+) 186, 158; IR: 2975, 2210, 1720, 1600, 1400, 1330 cm^{-1}; H^1 NMR 1.85 (s, 6H), 7.4 (d, 2H), 7.8 (d, 2H).

2-[p-*Cyano phenyl*] *acetic acid ethyl ester* **16**. The reaction between **14** and the monoanion (**e**) 4 h, flask) gave, after work up [B] the compound **16** m.p. 90–93° (135 mg, 71%). Found C, 69.75; H, 5.93; N, 7.25; O, 16.61%. $C_{11}H_{11}NO_2$ requires C, 69.80; H, 5.86; N, 7.40; O, 16.90. MS *m/e* 189 (M^+), 161.144; IR: 2950, 2220, 1730, 1610, 1360 cm^{-1}; H^1 NMR 1.25 (t, 3H), 3.70 (s, 2H), 4.10 (q, 2H), 7.4 (d, 2H), 7.65 (d, 2H).

2-[p-*Cyano phenyl*] *acetoacetic ethyl ester* **17**. The reaction between **14** and the monoanion (**e**) (1 h, flask) gave, after acidic work up conditions [A] the compound **17** m.p. 97° (subl.) (165 mg, 71%). Found C, 67.32; H, 5.65; N, 6.32; O, 20.81%. $C_{13}H_{13}NO_3$ requires C, 67.50, H, 5.66: N, 6.0; O, 20.75. MS *m/e* 231 (M^+) 189, 185, 143; IR: 3000, 2210, 1720, 1640, 1330 cm^{-1}; H^1 NMR (enol form): 1.15 (t, 3H), 1.85 (s, 3H), 4.15 (q, 2H), 7.2–7.8 (m, 4H); (keto ester form): 1.25 (t, 3H), 2.25 (s, 3H), 4.25 (q, 2H), 4.85 (s, 1H); 7.2–7.8 (m, 4H).

2-*Malonic acid diethyl ester*), 3-*cyano-pyridine* **19**. The reaction between the 2-bromo, 3-cyano pyridine **18** and the monoanion (a) (3 h, flask) after work up [B] gave **19**: oil (235 mg, 90%). MS *m/e* 262.0954 (M^+) $C_{13}H_{14}N_2O_4$ requires 262.0954, 190, 145; IR: 2950, 2220, 1730, 1580, 1560 cm^{-1}; H^1 NMR 1.3 (t, 6H), 4.25 (q, 4H), 5.25 (s, 1H), 7.35 (dd, 1H), 8.0 (dd, 1H), 8.80 (dd, 1H).

2-(*Ethyl malonic acid diethyl ester*), 3-*cyano pyridine* **20**. The reaction between **18** and the monoanion (**b**) (10 min, flask) followed by work up [B] gave the compound **20**: oil, (266 mg, 92%); MS *m/e* 290.1263 (M^+) $C_{15}H_{18}N_2O_4$ requires 290.1266; IR 2950, 2215, 1730, 1580, 1560 cm^{-1}; H^1 NMR 0.90 (t, 3H), 1.3 (t, 6H), 2.6 (q, 2H), 4.3 (q, 4H), 7.35 (dd, 1H), 7.9 (dd, 1H), 8.6 (dd, 1H).

2-(*Cyanoacetic ethyl ester*), 3-*cyano pyridine* **21**. The reaction between **18** and the monoanion (c), (1 h, flask) after work up [B] gave **21** m.p. (MeOH) 215 (dec.); (175 mg, 80%). Found C, 61.11; H, 4.26; N, 19.50; O, 15.09%. $C_{11}H_{10}N_3O_2$ requires C, 61.39; H, 4.22; N, 19.52; O, 14.87. MS *m/e* 215 (M^+), 170, 143, 116; IR: 2200, 1620, 1580, 1460 cm^{-1}; H^1 NMR 1.25 (t, 3H), 4.20 (q, 4H), 6.90 (t, 1H), 8.35 (d, 2H).

2-*Acetonyl*-3-*cyano pyridine* **22**. The reaction between **18** and the monoanion (**d**) (2 h, flask) gave after acidic [A] or basic [B] conditions work up the compound **22** oil, (128 mg, 80%). MS *m/e* 160, 145, 118; H^1 NMR: 2.30 (s, 3H), 4.15 (s, 2H), 7.15 (dd, 1H), 7.80 (dd, 1H), 8.55 (dd, 1H).

2-(*Acetic acid ethyl ester*) 3-*cyano pyridine* **23**. The reaction between **18** and the monoanion (e) (45 min flask) under work up [A] or [B] gave **23**: oil (153 mg, 80%). MS *m/e* 190.0742 (M^+). $C_{10}H_{10}N_2O_2$ requires 190.0742; IR: 2950, 2220, 1730, 1580, 1560 cm^{-1}; H^1 NMR 1.32 (t, 3H), 4.10 (s, 2H), 4.23 (q, 2H), 7.35 (dd, 1H), 8.0 (dd, 1H), 8.75 (dd, 1H).

2-(2-*Methyl acetoacetic ethyl ester*) 3-*cyano pyridine* **24**. The reaction between **18** and the monoanion (g) (30 min flask), after work up [B] afforded **24**: oil, (167 mg, 82%) MS *m/e* 204.0898 (M^+). $C_{11}H_{18}N_2O_2$ requires 204.089. IR: 2950, 2220, 1730, 1580, 1560 cm^{-1}; H^1 NMR 1.2 (t, 3H), 1.63 (d, 3H), 4.2 (q, 2H), 4.38 (q, 1H), 7.38 (dd, 1H), 8.0 (dd, 1H), 8.80 (dd, 1H).

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