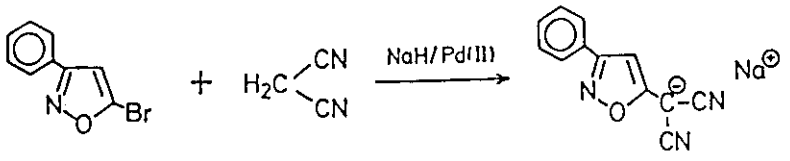
FORMATION AND REACTIVITY OF HIGHLY STABILIZED CARBANIONS AND ENOLATES BY Pd-CATALYZED ALKYLATION OF HETEROCYCLIC COMPOUNDS

Tsutomu Sakakibara*, Takashi Kume, Kumiko Shimohara, Hiroshi Fujishima, Shunpei Hara, and Toshifumi Shimoda

Institute of Chemistry, College of Liberal Arts, Kagoshima University, Korimoto, Kagoshima 890, JAPAN

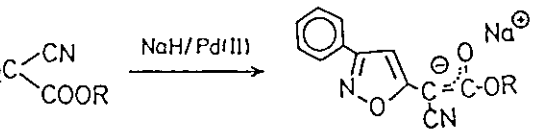
Abstract - Highly stabilized carbanion and enolate salts, heterocycle-substituted sodiomalononitrile and sodiocyanoacetates, were synthesized via Pd-catalyzed ring-alkylation of bromoheterocyclic compounds and shown to be useful intermediates for the synthesis of various alkyl-substituted heterocyclic compounds.

Alkylated hetero-5- or 6-membered rings are often very important for the synthesis of natural products or biologically active compounds.[1] For instance, 5-alkylisoxazoles are known to be effective drugs[1a-k] and key intermediates for natural product syntheses,[2] and generally to be synthesized via inter- or intramolecular cyclization of acyclic materials involving appropriate substituents.[3] Variously substituted alkylthiophenes also afford useful routes to complex aliphatic compounds via their reductive desulphurisation.[4] Therefore, direct alkylation onto heterocyclic rings is considered to give a useful route to biologically or synthetically important alkylated heterocycles. Recent publications have presented several convenient methods for the direct introduction of alkyl groups on aromatic or olefinic carbons.[5] We studied the reactions of some 5- and 6-membered bromoheterocycles with carbanions of active methylene compounds in the presence of Pd-catalyst, and isolated carbanion or ester enolate salts surprisingly stable to air and moisture.[6] The salts were reactive enough to give carbon-elongated products by alkyl halides in a polar solvent.



(1)

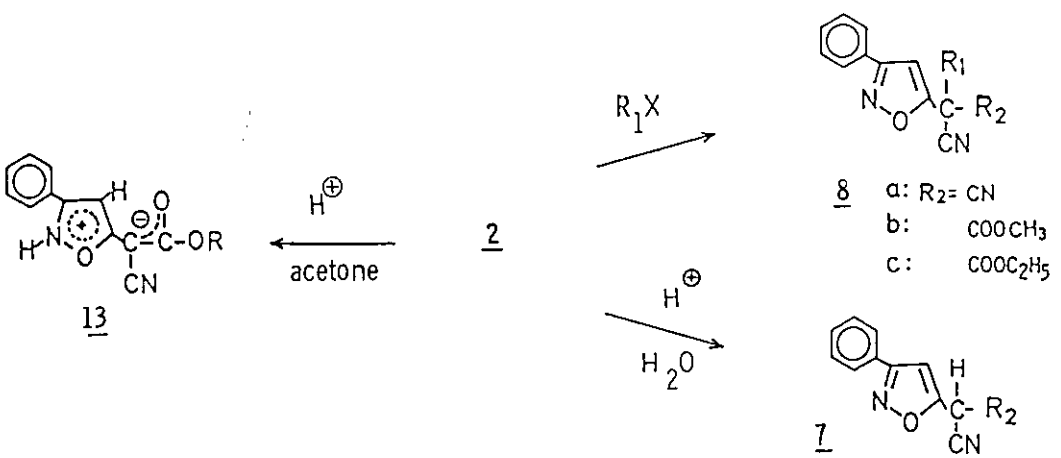
1 → 2a



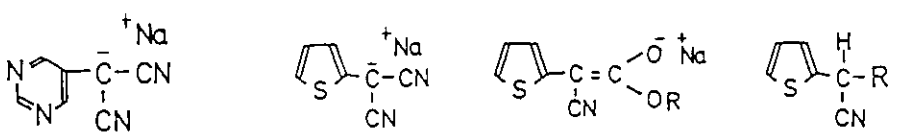
(2)

2 b: R=CH_3
c: R=C_2H_5

In a typical experiment, palladium-catalyzed reaction of 5-bromo-3-phenylisoxazole (**1**) with sodiomalononitrile in tetrahydrofuran at 60 ℃ for 7.5 h was carried out in the presence of excess sodium hydride. After the usual treatment, extraction of the aqueous mixture of products at pH 7 with ethyl acetate gave sodio(3-phenylisoxazol-5-yl)malononitrile (**2a**) in 94 % yield. The compound **2a** showed the two absorptions at 2165 and at 2205 cm^{-1} on the ir spectrum, attributed to cyano groups, ^1H-nmr signal at 5.68 ppm assigned to 4-C proton of



8 a: R_2= CN
b: $COOCH_3$
c: $COOC_2H_5$



4a **6a** **6b, c** **12 a, b, c**

the isoxazole ring, and a parent peak at m/z 231 on the mass spectrum. In the similar reactions of **1** with methyl and ethyl cyanoacetates, the corresponding coupling products (**2b** and **2c**) were isolated in 72 % and 83 % yields, respectively. Their nmr spectra gave the signals of alkoxy groups and 3-phenylisoxazole ring. **2b** and **2c** also showed the absorption of cyano groups at 2180 and 2170 cm^{-1}, respectively, but no ester absorption on their ir spectra. Thus they must exist as sodium ester enolates of (3-phenylisoxazol-5-yl)-cyanoacetates. These structures are supported by their nmr spectra which gave a considerably large paramagnetic shift of 4-C proton on the isoxazole rings (0.61-0.62 ppm, compared with that of **2a**) due to an expansion of the π - conjugation. The isolated salts, **2a**, **2b** and **2c**, were much more stable to air

Table 1. Pd-Catalyzed Alkylation of Bromoheterocycles

Heterocycle	Reactants[a] $PdX_2(PPh_3)_2$	M-H	$CH_2R(CN)$	Products isolated at pH 7[b] Carbanion(or Enolate)		C-H product	
1	X=Cl	NaH	R= CN	**2a**	94 %	none	
	Cl	NaH	$COOCH_3$	**2b**	72	none	
	Cl	NaH	$COOC_2H_5$	**2c**	83	none	
3	Cl	NaH	R= CN	**4a**	98	none	
	Cl	NaH	$COOCH_3$	**4b**	34	none	
	Cl[c]	NaH	$COOCH_3$	**4b**	19	none	
	OAc	NaH	$COOCH_3$	**4b**	28	none	
	OAc	LiH	$COOCH_3$	**4b**	35	none	
	OAc[c]	LiH	$COOCH_3$	**4b**	42	ND[d]	
	Cl	NaH	$COOC_2H_5$	**4c**	55	none	
	Cl[c]	NaH	$COOC_2H_5$	**4c**	35	ND[d]	
	Cl	LiH	$COOC_2H_5$	**4c**	46	none	
	OAc	NaH	$COOC_2H_5$	**4c**	58[e]	**11c**	25[e]
	OAc	LiH	$COOC_2H_5$	**4c**	53	**10c**	9.4
5	Cl	NaH	R= CN	**6a**	11	**12a**	62
	Cl	NaH	$COOCH_3$	**6b**	29	**12b**	38
	Cl	NaH	$COOC_2H_5$	**6c**	13	**12c**	21

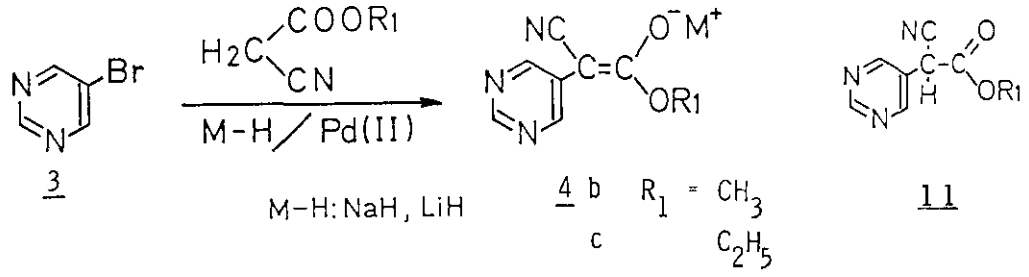
a. $PdX_2(PPh_3)_2$ (5 mol%) was used as a catalyst.
b. Yields are based on used Br-heterocycles.
c. Repeated experiment under the same conditions as just above experiment.
d. *Not determined.*
e. Products isolated from the aqueous product mixture at pH 3.

and moisture than the known carbanion salts.[6] The solid state-carbanion salts, after being stored in a refrigerator at 2 to 3 °C for two months, showed the same ir and nmr spectra as those of the freshly prepared materials. The results of the analogous reactions of 5-bromopyrimidine (**3**) and 2-bromothiophene (**5**) are summarized in Table 1. The alkylated products involving ester groups also were isolated in the enolate form, since they showed no ester absorption on the ir spectra in spite of the nmr observation of alkoxyl groups. Although all reactions were carried out under completely drying conditions and by usual syringe-work, the reactions using sodium hydride did not give constant yields of the sodium salts in the repeated experiments, presumably owing to the sensitivity to moisture. The use of lithium hydride in place of sodium hydride gave the corresponding lithium salts constantly in good yields, as shown in Table 1.

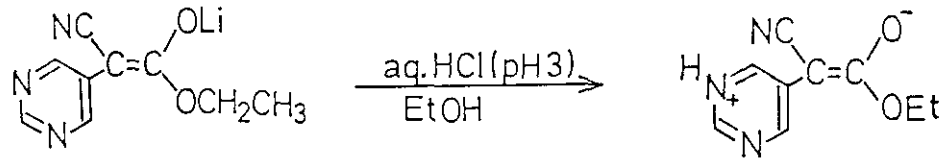
The aqueous solution of these carbanion (or enolate) salts, **2a** and **2c**, gave the corresponding α-C protonated products (**7a** and **7c**) in almost quantitative yields by the ethyl acetate extraction at pH 1, after an acidification with hydrochloric acid. The protonated product from the enolate **2c** showed an ester absorption at near 1760 cm^{-1} on its ir spectrum. In the case of thiophene derivatives, the yields of the sodium salts (**6**) were lower than those of others (**2** and **4**) as shown in Table 1, indicating that **6** was considerably protonated even at pH 7. Recent publication[7] describes that pyridine ring causes the activation of ring C-methyl groups toward carbanion formation. The present results evidently support that the heterocycles such as pyrimidine and isoxazole rings also result in the stabilization of the anions on the side chain. **7a** showed ^{1}H-nmr signals of 4-H of isoxazole ring and α-methine H at 6.76 ppm and 4.60 ppm (br.) in $C_2D_2Cl_4$, respectively, while the corresponding signals in d_4-methanol were completely absent. Similarly, **7c** had the absorption signals of 4-H and α-H at 6.63 and 4.93 ppm in $CDCl_3$, respectively, but the addition of D_2O to the solution caused the gradual disappearance of the 4-H and α-H absorptions. The results may show ready deuterium exchange on 4- and α-positions of the compounds **7**. The high reactivity of 4-H proton in **2** was also shown in the bromination of **2c**. Namely, the reaction of **2c** with bromine in carbon tetrachloride gave 4-bromo-2-phenylisoxazol-5-ylcyanoacetate (**9**) as major product (40%).

The alkylation of **3** with ethyl cyanoacetate using lithium hydride and palladium catalyst gave the N-protonated product **10c**, which was considered to involve the zwitterionic structure, along with the usual lithium enolate (**4c**-Li). The structure of **10c** was supported by the result of ^{13}C-nmr measurement and the fact that

the protonation of the lithium enolate **4c**-Li at pH 3 gave the identical compound (31.3 %). The ^{1}H-nmr spectrum of **10c** showed considerably large paramagnetic shift for pyrimidine ring-Hs (0.46-0.68 ppm) and ethoxy methylene (0.17 ppm), compared with those of **4c**-Li, and showed the N-H signal at very low field (at 15.0 ppm). On the other hand, **2b** and **2c** dissolved in acetone showed an interesting behavior by the addition of trifluoroacetic acid. The nmr measurement of **2c** in d_6-acetone gave 4-H signal at 6.29 ppm, but after the addition of a few drops of trifluoroacetic acid, the signal was shifted paramagnetically to 7.13 ppm. **2b** also showed the similar behavior (at 6.40 ppm to 7.08 ppm). The attempted isolation of the formed products(λ_{max} in acetone; 319.2 nm) gave a pale yellow solid after the addition of trifluoroacetic acid to **2c**, but the solid was



3 4 b R_1 = CH_3 c C_2H_5 11



4c-Li 10c

insoluble in most of organic solvents after the isolation, probably due to the polymerization. The quaternalized isoxazole rings are known to show the nmr signals of 4-Hs in lower region than at 7.0 ppm, as can be seen in the case of Woodward reagents K and L, which give them at 7.56 and at 7.00 ppm, respectively.[8] Thus, the intermediates formed in acetone/trifluoroacetic acid *in situ* may be considered to be mesoionic (or zwitter ionic) compounds **13** from the analogy to **10c**.[9]

The carbanion or enolate salts **2** were reactive enough to give carbon-elongated products by the treatment with various alkyl halides at higher temperatures.

Table 2. Alkylation of Carbanion and Enolate Salts **2**

2	Reagents[a] R_1X	Solvent[b]	Temp. °C	Time hr	Product **8**,	% [c]
2a	CH_3I	C_2H_5OH	70	7	**8a**(R_1=CH_3),	66.0
2a	C_2H_5I	C_2H_5OH	70	7	**8a**(C_2H_5),	48.1
2a	C_2H_5I	DMF	70	7	**8a**(C_2H_5),	73.0
2b	C_2H_5I	DMF	80	4	**8b**(C_2H_5),	79.8
2b	n-C_3H_7Cl	DMF	60	7	**8b**(n-C_3H_7),	16.4
2b	C_2H_5I	DMI	70	8	**8b**(C_2H_5),	81.0
2c	i-C_3H_7I	DMF	70	8	**8c**(i-C_3H_7),	11.2
2c	i-C_3H_7I	DMI	80	4	**8c**(i-C_3H_7),	69.1
2c	t-$C_4H_{10}Cl$	DMF	80	8	**8c**(t-C_4H_{10}),	none

a. In a typical experiment, **2** (0.1 mmol) and R_1X (0.2 mmol) were used.
b. Ethanol (10 ml), DMF (4 ml), or DMI (4 ml) was used as a solvent.
c. Yields are based on used **2**.

The results of the reactions of **2** with various alkyl halides in polar solvents are summarized in Table 2. Primary or secondary alkyl iodides were good alkylating reagents of the carbanions or enolate salts. Alkyl chlorides showed relatively low reactivity and t-butyl iodide resulted in no alkylation probably due to steric repulsion of the bulky alkyl group. Dimethylformamide (DMF) and 1,3-dimethyl-2-imidazolidinone (DMI) were effective solvents for the alkylation of **2**. Therefore, the present double alkylating method via the carbanion or enolate salts is considered to give a promising method for the synthesis of various long chain alkyl-substituted heterocyclic compounds.

Consequently, bromoheterocyclic compounds were confirmed to be successfully alkylated by active methylene carbanions in the presence of palladium catalyst and to give the highly stabilized carbanions or the enolate salts. Especially, the reactivity of the carbanion or enolate salts containing isoxazole ring was investigated with alkyl halides and with proton in detail. The result showed that the salts were active enough to give carbon-elongated products. Moreover, the acidification of the carbanion or enolate salts containing nitrogen-heterocycles was found to result in the competitive or regioselective protonation on the ring nitrogen or on the side chain α-carbon, depending on the reaction conditions.

EXPERIMENTAL

All melting points were measured by using a Yanagimoto mp apparatus and were uncorrected. Uv spectra were recorded on a Hitachi 228 double beam spectrophotometer. Ir spectra were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were taken on JEOL PMX-60 and JNM-EX-90 instruments, respectively. Chemical shifts are given as values from tetramethylsilane as an internal standard. Ms were recorded with a JEOL JMS-01SG mass spectrometer.

Bis(triphenylphosphine)palladium(II) chloride and acetate were synthesized by the reaction of commercial palladium(II) chloride and acetate, respectively, with triphenylphosphine in acetonitrile.

5-Bromo-3-phenylisoxazole was synthesized according to the method described in literature.[10] 5-Bromopyrimidine and 2-bromothiophene were commercially available and used after recrystallization or distillation.

Sodio(3-phenylisoxazol-5-yl)malononitrile (2a)

To the THF (20 ml) solution of sodium hydride (1.73 g of the 50% oil suspension which was washed with THF four times; 36 mmol), malononitrile (1.19 g, 18 mmol) dissolved in THF (13 ml) was added dropwisely. To the resulting mixture, the THF solution (4 ml) of 5-bromo-3-phenylisoxazole (**1**, 1.35 g, 6 mmol) and subsequently bis(triphenylphosphine)palladium(II) chloride (210 mg, 0.3 mmol) were added and stirred at 60°C for 7.5 hr under nitrogen atmosphere. The complete consumption of **1** was confirmed by tlc. The reaction products were poured on ice-water mixture and the aqueous solution was adjusted at pH 7 by 1 M hydrochloric acid. The extraction with ethyl acetate and subsequent work-up of the extract gave 1.3 g of almost pure **2a** as pale brown solid (94% based on **1**). Further purification was performed by preparative tlc, using silica gel and developed by $CHCl_3$-MeOH (8:2). The 0.1M aqueous solution of **2a** gave white precipitates by an addition of 0.05M potassium pyroantimonate solution, showing the presence of sodium ions.

2a was characterized as follows: mp 220°C decomp, ir (KBr, cm^{-1}); ν 2205, 2165, 1580(br), 1480, 1420, 960, 735, 685. ^{1}H-Nmr (d_6-acetone, TMS); δ (ppm) 5.68 (s, 1H, 4-H), 7.26-7.53 (m, 3H, aromatic H), 7.68-7.97(m, 2H, aromatic H)). Ms; m/z 231 (M^+). Anal. Calcd for $C_{12}H_6N_3ONa$: C, 62.34; H, 2.62; N, 18.18. Found: C, 62.63; H, 2.34; N, 18.26.

Methyl Sodio(3-phenyl-5-isoxazolyl)cyanoacetate (2b) and Ethyl Sodio(3-phenyl-5-isoxazolyl)cyanoacetate (2c)

The reaction of **1** with methyl cyanoacetate or ethyl cyanoacetate in the presence of bis(triphenylphosphine)palladium(II) chloride was carried out and treated in the same procedure as described above. **2b** and **2c** were isolated in the yields of 72 % and 83 %, respectively. The yields are based on the used **1**.

2b: mp 180 °C decomp, ir (KBr, cm^{-1}); ν 2180, 1560 (br), 1440, 1410, 1355, 1185, 1140, 1035, 755, 723, 680. ^{1}H-Nmr (d_6-acetone, TMS); δ (ppm) 3.62 (s, 3H, $-CH_3$), 6.40 (s, 1H, 4-H), 7.32-7.45 (m, 3H, aromatic H), 7.69-7.82 (m, 2H, aromatic H). Ms; m/z 264 (M^+). Anal. Calcd for $C_{13}H_9N_2O_3Na$: C, 59.10; H, 3.43; N, 10.60. Found: C, 58.80; H, 3.74; N, 10.76.

2c: mp 160 °C decomp, ir (KBr, cm^{-1}); ν 2170, 1560(br), 1460, 1415, 1330, 1155, 1095, 1040, 758, 686. ^{1}H-Nmr (d_6-acetone, TMS); δ (ppm) 1.33 (t, J=7.2 Hz, 3H, $-CH_3$), 4.13 (q, J=7.2 Hz, 2H, $-CH_2-$), 6.53 (s, 1H, 4-H), 7.17-7.83 (m, 5H). Ms; m/z 278 (M^+). Uv (acetone, nm); λ_{max} 212.6 (ε 1.03×10^4), 330.0 (br)(ε 5.46×10^3). Anal. Calcd for $C_{14}H_{11}N_2O_3Na$: C, 60.03; H, 3.99; N, 10.07. Found: C, 59.09; H, 4.36; N, 10.11.

Protonation of 2

The carbanion salt **2a** (0.40 g, 1.7 mmol) was dissolved in 30 ml of water and the resulting solution was adjusted at pH 1 by 1 M hydrohloric acid. The extraction of the aqueous solution with ethyl acetate gave 3-phenyl-5-isoxazolylmalononitrile (**7a**, 330 mg, 92 %) as pale yellow powder, which was characterized as follows: **7a**: mp 141-143 °C decomp, ir (KBr, cm^{-1}); ν 2201, 2182(sh), 1608, 1473, 1445, 1415, 912, 775, 693. ^{1}H-Nmr ($C_2D_2Cl_4$, TMS); δ (ppm) 4.60 (br s, 1H, α-H), 6.76 (s, 1H, 4-H), 7.10-7.90 (m, 5H, aromatic H). Ms (relative intensity); m/z 209 (M^+, 52.9), 144 (100), 116 (21.4), 77 (64.3). High-resolution ms (hrms); calcd for $C_{12}H_7N_3O$: 209.0589; found: 209.0575.

The protonation of **2c** was carried out in the same manner as described above, and gave ethyl 3-phenyl-5-isoxazolylcyanoacetate (**7c**) as a pale yellow liquid in the yield of 87 %.

7c: liq., ir (KBr, cm^{-1}); ν 1758, 1605, 1463, 1441, 1402, 1250, 1025, 910, 768, 686. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.18 (t, J=7.1 Hz, 3H, $-CH_3$), 4.18 (q, J=7.1 Hz, 2H, $-CH_2-$), 4.92 (s, 1H, α-H), 6.62 (s, 1H, 4-H), 7.10-7.90 (m, 5H, aromatic H). Ms (relative intensity); m/z 256 (M^+, 65.5), 184(100), 144(85.0), 77(83.2). Hrms ; Calcd for $C_{14}H_{12}N_2O_3$: 256.0847. Found: 256.0820.

After the nmr spectra of **2b** and **2c** were measured in d_6-acetone, a few drops of trifluoroacetic acid were added into each solution. Then the remeasurement of the samples gave the following data; **2b**: ^{1}H-Nmr (d_6-acetone/CF_3COOH, TMS); δ

(ppm) 3.83 (s, 3H), 7.08 (s, 1H), 7.33-7.56 (m, 3H), 7.72-8.00 (m, 2H). **2c**: ^{1}H-Nmr (d_6-acetone/CF_3COOH, TMS); δ (ppm) 1.03 (t, J=7.4 Hz, 3H), 4.34 (q, J=7.4 Hz, 2H), 7.13 (s, 1H), 7.31-7.68 (m, 3H), 7.71-8.02 (m, 2H).

The enolate salt **2c** (50 mg, 0.18 mmol) was dissolved in acetone (35 ml), and then trifluoroacetic acid (45 mg, 0.4 mmol) was added to the resulting solution. After a few min, a pale yelow solid (**13c**) was precipitated and filtered out. The isolated solid was almost insoluble in most of organic solvents and thus could not be purified furthermore. **13c**: mp >200 °C decomp, ir (KBr, cm^{-1}); ν 2150, 1670, 1550, 1475, 1400, 1132, 1025, 765, 683. ^{1}H-Nmr of **13c** in solution are shown above. Uv (acetone); λ_{max} 319.2 nm.

Alkylation of 2

The sodium salt **2a** (0.30 g, 1.3 mmol) and methyl iodide (0.94 g, 6.6 mmol) were dissolved in ethanol (3.5 ml) and the mixture was stirred at 70° C for 7 h under nitrogen atmosphere. The reaction mixture was poured into 10 ml of water and extracted with 7 ml of ethyl ether four times. The extract gave a white solid, which was purified by the silica gel chromatography with elution by chloroform and further by the recrystalization from ethanol-water (9:1). Methyl(3-phenylisoxazol-5-yl)malononitrile (**8a**, $R_1 = CH_3$) was obtained as colorless plates (171 mg, 66 %). A similar alkylation of **2a** (0.20 g, 0.84 mmol) with ethyl iodide (0.20 g, 1.3 mmol) gave ethyl(3-phenylisoxazol-5-yl)malononitrile (**8a**, $R_1 = C_2H_5$, 137 mg, 73 %).

8a ($R_1 = CH_3$): mp 66.5-66.8 °C, ir (KBr, cm^{-1}); ν 1983 (w), 1608, 1477, 1442, 1407, 1179, 1113, 910, 778, 699. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 2.23 (s, 3H, $-CH_3$), 6.84 (s, 1H, 4-H), 7.40-7.97 (m, 5H, aromatic H). Ms: m/z 223 (M^+). Uv (CH_3CN, nm); λ_{max} 224.6 (ε 11800). Anal. Calcd for $C_{13}H_9N_3O$: C 69.95, H 4.07, N 18.83. Found: C 69.83, H 3.94, N 18.77.

8a ($R_1 = C_2H_5$): mp 50.6-51.5 °C, ir (KBr, cm^{-1}); ν 1983 (w), 1608, 1470, 1442, 1407, 1142, 1110, 1003, 920, 773, 690. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.30 (t, J=7.1 Hz, 3H, $-CH_3$), 2.53 (t, J=7.1 Hz, 2H, $-CH_2-$), 6.84 (s, 1H, 4-H), 7.33-7.95 (m, 5H, aromatic H). Ms; m/z 237 (M^+). Uv (CH_3CN, nm); λ_{max} 244.4 (ε 13000). Anal. Calcd for $C_{14}H_{11}N_3O$: C 70.86, H 4.67, N 17.71. Found: C 70.77, H 4.53, N 17.68.

Similar reactions of **2b** *or* **2c** *with ethyl iodide, n-propyl chloride, or iso-propyl iodide gave methyl ethyl(3-phenylisoxazol-5-yl)cyanoacetate (***8b**, $R_1 = C_2H_5$), methyl n-propyl(3-phenylisoxazol-5-yl)cyanoacetate (**8b**, $R_1 = n\text{-}C_3H_7$), or ethyl isopropyl(3-phenylisoxazol-5-yl)cyanoacetate (**8c**, $R_1 = iso\text{-}C_3H_7$).

8b (R_1= C_2H_5): liq, ir (neat, cm^{-1}); ν 2320, 1745, 1235, 905, 760, 685. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 0.98 (t, J=6.6 Hz, 3H, $-CH_3$), 2.41 (q, J=6.6 Hz, 2H, $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 6.57 (s, 1H, 4-H), 7.23-7.50 (m, 5H, aromatic H). Ms; m/z 270 (M^+). Hrms; calcd for $C_{15}H_{14}N_2O_3$: 270.1003; found: 270.0990.

8b (R =n-C_3H_7): liq, ir (neat, cm^{-1}); ν 2325, 1745, 1230, 905, 760, 685. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.01 (t, J=6.6 Hz, 3H, $-CH_3$), 1.10-1.80 (m, 2H, $-CH_2$ -), 2.46 (t, J=6.6 Hz, 2H, $-CH_2-$), 4.00 (s, 3H, $-OCH_3$), 6.92 (s, 1H, 4-H), 7.30-7.73 (m, 5H, aromatic H). Ms; m/z 284 (M^+). Hrms; calcd for $C_{16}H_{16}N_2O_3$: 284.1161; found: 284.1135.

8c (R_1=i-C_3H_7): liq, ir (neat, cm^{-1}); ν 2250, 1750, 1468, 1440, 1402, 1235, 1030, 910, 765, 725, 683. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.10 (dd, J=6.4 and 9.6 Hz, 6H, $-CH_3$), 1.32 (t, J=6.7 Hz, 3H, $-CH_3$), 2.97 (sep, J=6.4 Hz, 1H, -CH-), 4.30 (q, J=6.7 Hz, 2H, $-CH_2-$), 6.78 (s, 1H, 4-H), 7.28-7.90 (m, 5H, aromatic H). Ms; m/z 298 (M^+). Hrms; calcd for $C_{17}H_{18}N_2O_3$: 298.1239; found: 298.1255.

The reaction of **2b** (100 mg, 0.38 mmol) with t-butyl chloride (234 mg, 2.5 mmol) was carried out in DMF (10 ml) at 80 °C for 5 h. After the usual work-up, the silica gel column chromatography of the reaction mixture with benzene-ethyl acetate gave 3-phenyl-5-isoxazolylacetonitrile as colorless needles (49 mg, 86.0 %), which was characterized as follows: mp 67.0-68.0 °C, ir (KBr, cm^{-1}); ν 3100, 2320, 1605, 1463, 1410, 1155, 1002, 913, 822, 760, 685. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 3.93 (s, 2H, $-CH_2-$), 6.64 (s, 1H, 4-H), 7.23-7.73 (m, 5H, aromatic H). Ms; m/z (relative intensity) 184 (M^+, 45.2), 144 (100), 116 (21.6), 77 (51.3). Hrms; calcd for $C_{11}H_8N_2O$: 184.0637; found: 184.0660. However, the alkylated product **8b** (R =t-C_4H_9) could not be isolated.

Bromination of 2c with Bromine.

To the carbon tetrachloride solution (5 ml) of **2c** (280 mg, 1 mmol), 10% carbon tetrachloride solution (7.5 ml) of bromine was dropwise added under stirring at 5 °C, until the decolorization of bromine ceased. After the usual work-up of the reaction mixture, the pale yellow oil was isolated, along with 31 mg of **2c**. The column chromatography of the oil twice using silica gel with benzene-ethyl acetate gave ethyl (4-bromo-3-phenylisoxazol-5-yl)cyanoacetate (**9**) as a colorless liquid (120 mg, 40 %).

9: ir (neat, cm^{-1}); ν 1760, 1608, 1260, 1210, 1150, 1058, 1025, 920, 860, 765, 690. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.33 (t, J=7.2 Hz, 3H, $-CH_3$), 4.37 (q, J=7.2 Hz, 2H, $-CH_2-$), 5.15 (s, 1H, α-H), 7.30-8.00 (m, 5H, aromatic H). Ms; m/z (relative intensity) 336 (M^+, 19.9), 334 (M^+, 19.7), 224 (45.3), 222 (45.1), 143

(37.1), 77 (100).

Sodio(5-pyrimidinyl)malononitrile (4a), Methyl 5-Pyrimidinylcyanoacetate Sodium Enolate (4b) and Ethyl 5-Pyrimidinylcyanoacetate Sodium Enolate (4c)

Sodio(5-pyrimidinyl)malononitrile (**4a**) and methyl or ethyl 5-pyrimidinylcyanoacetate sodium enolate (**4b** or **4c**) were synthesized from the reaction of 5-bromopyrimidine (**3**) with malononitrile and methyl or ethyl cyanoacetate using sodium hydride and bis(triphenylphosphine)palladium(II) chloride or acetate, analogously to the method described in the synthesis of **2**.

4a: mp 227-230 °C decomp, ir (KBr, cm^{-1}); ν 2170, 1560 (br), 700. ^{1}H-Nmr (d_4-MeOD, TMS); δ (ppm) 8.20 (s, 2H, 4,6-H), 8.33 (s, 1H, 2-H). Anal. Calcd for $C_7H_3N_4Na$; N, 33.73; Na, 13.84. Found: N, 33.36; Na, 14.12.

4b: mp 179-184 °C decomp, ir (KBr, cm^{-1}); ν 2180, 1550 (br), 710, no ester absorption. ^{1}H-Nmr (d_4-MeOD, TMS); δ (ppm) 3.98(s, 3H, $-OCH_3$), 8.35 (s, 1H, 2-H), 8.87 (s, 2H, 4,6-H). Anal. Calcd for $C_8H_6N_3O_2Na$: N, 21.10; Na, 11.54. Found: N, 21.43; Na, 11.29.

4c: mp 270-271 °C decomp, ir (KBr, cm^{-1}); ν 2160, 1550 (br), 710, no ester absorption. ^{1}H-Nmr (d_4-MeOD, TMS); δ (ppm) 1.26 (t, J=7.2 Hz, 3H, $-CH_3$), 4.09 (q, J=7.2 Hz, 2H, $-OCH_2-$), 8.34 (s, 1H, 2-H), 8.89 (s, 2H, 4,6-H). Anal. Calcd for $C_9H_8N_3O_2Na$: N, 19.71; Na, 10.79. Found: N, 20.10; Na, 10.35.

Ethyl (1-Protopyrimidinium-5-yl)cyanoacetate Enolate Anion (10c)

The reaction of **3** (4.0 mmol) with ethyl cyanoacetate (15 mmol) in the presence of lithium hydride (60 mmol) and bis(triphenylphosphine)palladium(II) acetate (0.45 mmol) at 70 °C for 3 h in THF (20 ml) gave 9.4 % yield of **10c**, together with ethyl (5-pyrimidinyl)cyanoacetate lithium enolate (**4c**-Li, 53 %). After the lithium enolate (**4c**-Li) dissolved in ethanol (50 ml) was treated with aqueous hydrochloric acid (pH 3), the extraction of the reaction mixture with ethyl acetate gave **10c** in the yield of 31.3 % (based on the used **4c**-Li).

10c: ir (KBr, cm^{-1}); ν 2200, 1650, 1605, 1545, 1400, 1250, 1052, 1022, 898, 763, no ester absorption. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.36 (t, J=7.2 Hz, 3H, $-CH_3$), 4.27 (q, J=7.2 Hz, 2H, $-CH_2-$), 8.18-8.32 (m, 3H, pyrimidine H), 15.0 (br.s, 1H, N-H). ^{13}C-Nmr ($CDCl_3$, TMS); δ (ppm) 12.77 ($-CH_3$), 60.50 ($-CH_2-$), 109.25 (=C-), 144.22 (2-C), 151.77 (=C-), 155.23 (4,6-C), 169.28 (5-C), 189.72 (C-N). Anal. Calcd for $C_9H_9N_3O_2$; C 42.36, H 3.55, N 16.47. Found; C 42.72, H 3.83, N 16.16.

4c-Li: ir (KBr, cm^{-1}); ν 2160, 1610, 1550, 1425, 1375, 1337, 1298, 1120, 1042, 710. ^{1}H-Nmr (d_6-acetone, TMS); δ (ppm) 1.91 (t, J=7.2 Hz, 3H, $-CH_3$), 4.10 (q, J=7.2 Hz, 2H, $-CH_2-$), 7.50-7.86 (m, 3H, pyrimidine H). ^{13}C-Nmr (d_6-acetone,

TMS); δ (ppm) 14.9 ($-CH_3$), 61.0 ($-CH_2-$), 110.2 (=C), 135.9 (=C), 150.0 (2-C), 150.1 (4,6-C), 170.4 (5-C), 207.3 (C-N).

Sodio(2-thiophenyl)malononitrile (6a), Methyl 2-Thiophenylcyanoacetate Sodium Enolate (6b), and Ethyl 2-Thiophenylcyanoacetate Sodium Enolate (6c)

Similar reactions of 2-bromothiophene with malononitrile and methyl or ethyl cyanoacetate in THF in the presence of sodium hydride and palladium catalyst gave the carbanion salt **6a** and the sodium enolate **6b** or **6c**, in the yields shown in Table 1.

6a: mp >298 °C decomp, ir (KBr, cm^{-1}); ν 2180, 1540, 680. ^{1}H-Nmr (d_6-acetone, TMS); δ (ppm) 7.70-8.15 (m, 3H, Ar-H). Anal. Calcd for $C_7H_3N_2SNa$: Na 13.51. Found; Na 13.39.

6b: mp 123-128 °C decomp, ir (KBr, cm^{-1}); ν 2150, 1430, 680, no ester. ^{1}H-Nmr (d_4-MeOD, TMS); δ (ppm) 3.77 (s, 3H, $-OCH_3$), 7.33-7.67 (m, 3H, Ar-H). Anal. Calcd for $C_8H_6NO_2SNa$: Na 11.31. Found: Na 11.20.

6c: mp 128-131 °C decomp, ir (KBr, cm^{-1}); ν 2190, 1420, 680, no ester. ^{1}H-Nmr ($CDCl_3$, TMS); δ (ppm) 1.25 (t, J = 6.7 Hz, 3H, $-CH_3$), 4.25 (q, J = 6.7 Hz, 2H, $-CH_2-$), 7.37-7.68(m, 3H, Ar-H). Anal. Calcd for $C_9H_8NO_2SNa$: Na 10.58. Found: Na 10.28.

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