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Activated Nitriles in Heterocyclic Synthesis: A Novel Synthesis of Polyfunctinally Substituted Pyridine Derivatives

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Summary. A variety of polyfunctionally substituted pyridines were prepared by reacting enaminonitriles with formaldehyde and active methylene reagents or cinnamonitrile derivatives.

Keywords. Enaminonitrile; Formaldehyde; Benzothiazoleacetonitrile; Cinnamonitriles; Pyridines.

Aktivierte Nitrile in der Heterocyclensynthese

Zusammenfassung. Eine Reihe von polyfunktionell substituierten Pyridinen wurde durch Reaktion von Enaminonitrilen mit Formaldehyd und aktiven Methylenreagenzien oder Cinnamonitrilen dargestellt.

Introduction

Aldehydes condense with active methylene nitriles to yield the corresponding ylidene derivatives [1]. The reaction of these ylidenes with active methylene [2, 3] and active methyl [4] reagents has been extensively utilized for the synthesis of 4*H*-pyrans, 4*H*-thiopyrans, pyridines, and benzene derivatives. Although α-functionally substituted acrylonitriles are expected to react similarly with active methylene reagents affording substituted pyrans, thiopyrans, pyridines, and benzenes, reactions of this type have not been reported to our knowledge with the exception of our recent report [5].

The difficulty of preparing α-functionally substituted acrylonitriles might explain the lack of reports on their utility. Recently we have shown that a mixture of 2-cyanomethyl-benzothiazole and formaldehyde generates methylene-2-cyano-methylbenzothiazole *in situ* and can thus be considered as a synthetic equivalent of this reagent [5].

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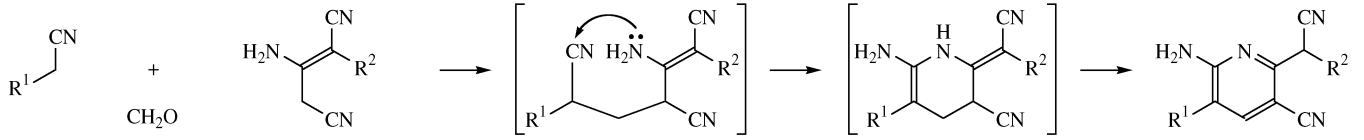
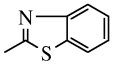
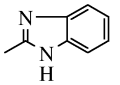


1 **2** **3** **4** **5**

1a: R^1 = 

1b: R^1 = 

1c: R^1 = 

1d: R^1 = 

1e: R^1 = CN

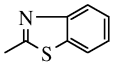
1f: R^1 = $-\overset{\overset{O}{\|}}{C}-Ph$

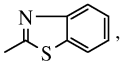
1g: R^1 = $-COOEt$

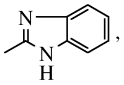
1h: R^1 = $-\overset{\overset{S}{\|}}{C}NH_2$

1i: R^1 = $-\overset{\overset{O}{\|}}{C}NH_2$

2a: R^2 = CN

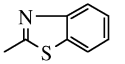
2b: R^2 = 

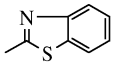
5a: R^1 =  , R^2 = CN

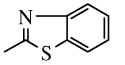
5b: R^1 =  , R^2 = CN

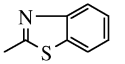
5c: R^1 =  , R^2 = CN

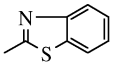
5d: R^1 =  , R^2 = CN

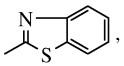
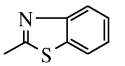
5e: R^1 = CN, R^2 = 

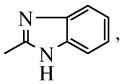
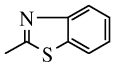
5f: R^1 = $-\overset{\overset{O}{\|}}{C}-Ph$, R^2 = 

5g: R^1 = $-COOEt$, R^2 = 

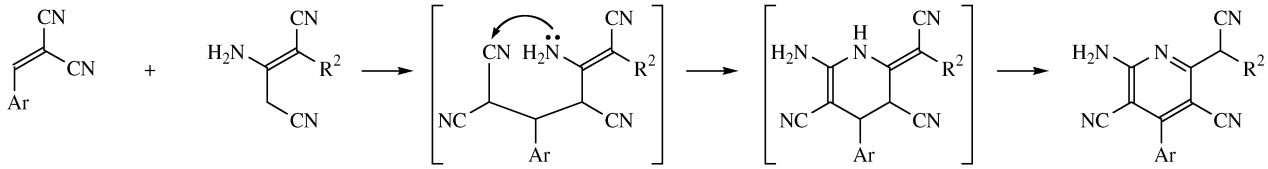
5h: R^1 = $-\overset{\overset{S}{\|}}{C}NH_2$, R^2 = 

5i: R^1 = $-\overset{\overset{O}{\|}}{C}NH_2$, R^2 = 

5j: R^1 =  , R^2 = 

5k: R^1 =  , R^2 = 

Scheme 1



6 **2** **7** **8** **9**

6a: Ar = C_6H_5
6b: Ar = C_6H_4-*o*-CH_3
6c: Ar = C_6H_4-*p*-NO_2
6d: Ar = C_6H_2-2,3,4-OCH_3
6e: Ar = C_5H_4N

2b: R^2 =

9a: Ar = C_6H_5, R^2 =
9b: Ar = C_6H_4-*o*-CH_3, R^2 =
9c: Ar = C_6H_4-*p*-NO_2, R^2 =
9d: Ar = C_6H_2-2,3,4-OCH_3, R^2 =
9e: Ar = C_5H_4N, R^2 =

Scheme 2

Results and Discussion

In the present paper we report the results of our work aiming at an investigation of the synthetic potentialities of this kind of reagent and related functionally substituted acrylonitriles. It was found that **2a** reacts with formaldehyde and 2-cyanomethyl-benzothiazole in boiling ethanol containing catalytic amounts of *TEA* to give 2-amino-3-benzothiazolyl-5-cyano-pyridin-6-yl-malononitrile (**5a**). Its structure was derived from elemental and spectroscopic analysis. The IR spectrum of **5a** showed absorption bands at 3450, 2207, and 1628 cm^{-1} corresponding to NH_2, CN, and C=N groups. Mass spectroscopic and analytical data were in agreement with structure **5a** (cf. Experimental). The formation of **5a** is assumed to proceed *via in situ* formation of the methylene derivative of the nitriles **1** which then add to **2** yielding the intermediate *Michael* adducts **3**. These spontaneously cyclize to **4** which develop to the final isolable products **5** (Scheme 1).

In the same way **1b–k** were reacted with **2a**, **b** to yield the pyridines **5b–k**. The structure of the products **5** was established as described above for **5a**.

We also found that heating a mixture of equimolar amounts of **2b** and cinnamonitriles **6a–e** in refluxing ethanol in the presence of *TEA* or piperidine affords the pyridine derivatives **9a–e**. The ^1H NMR spectrum of **9a** showed two signals at 3.5 and 6.7 ppm. The signal at 6.7 ppm disappeared upon addition of D_2O. Thus, these resonances were assigned to the CH–CN proton and the NH_2 function. It is assumed that **2b** adds to the double bond of **6** to give the intermediate *Michael* adducts **7a–e** which then spontaneously cyclize to the final isolable products **9** (Scheme 2).

Experimental

All melting points are uncorrected. FTIR spectra (KBr) were recorded on a Nicolet Magna Model 550 IR spectrophotometer. ^1H NMR spectra in $CDCl_3$ were determined on a Bruker WP spectrometer at 200 MHz with *TMS* as internal standard. Mass spectra were recorded at 70 eV with a Varian MAT 311 instrument. Elemental analyses (C. H. N) agree satisfactorily with the calculated values.

General procedure for the synthesis of 2-amino-5-cyano derivatives of pyridine (**5**)

Equimolar amounts of enaminonitrile **1** (4 mmol), formaldehyde (1 cm^3, 30% aqueous solution), and **2** (4 mmol) in 25 cm^3 ethanol were treated with a few drops of *TEA*. The reaction mixture was refluxed for 3 h and the solid product was recrystallized from the solvent given below.

2-Amino-3-benzoimidazolyl-5-cyanopyridin-6-yl-malononitrile (**5a**; $C_{16}H_{18}N_6S_2$)

From **1a** and **2a**; yield: 70% (*DMF*/ethanol); m.p.: 240°C: IR (KBr): $\bar{\nu}$ =3450 (NH_2). 2207 (CN), 1628 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 pyr), 7.8 (brs, NH_2), 7.2–7.6 (m, 4H, ar), 3.9 (s, CH–CN) ppm; MS: $m/z = 316$ (M^+).

2-Amino-3-benzoimidazolyl-5-cyanopyridin-6-yl-malononitrile (**5b**; $C_{16}H_9N_7$)

From **1b** and **2a**; yield: 68% (*DMF*/ethanol); m.p.: 270°C; IR (KBr): $\bar{\nu}$ = 3450 (NH_2), 2200 (CN), 1617 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.7 (s, NH), 8.2 (s, H_4 pyr), 7.8 (brs, NH_2), 7.16–7.54 (m, 4H ar), 3.9 (s, CH–CN) ppm; Ms: $m/z = 299$ (M^+).

2-Amino-3-pyridyl-5-cyanopyridin-6-yl-malononitrile (**5c**; $C_{14}H_8N_6$)

From **1c** and **2a**; yield: 65% (*DMF*/ethanol); m.p.: 220°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2202 (CN), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 Pyr), 7.8 (brs, NH_2), 7.3–7.65 (m, 4H ar), 3.9 (s, CH–CN) ppm; MS: $m/z = 260$ (M^+).

2-Amino-3-thienyl-5-cyanopyridin-6-yl-malononitrile (**5d**; $C_{13}H_7N_5S$)

From **1d** and **2a**; yield: 62% (*DMF*/ethanol); m.p.: 250°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2206 (CN), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.1 (s, H_4 pyr), 6.95–7.38 (m, 3H ar), 6.0 (brs, NH_2), 3.9 (s, CH–CN) ppm; MS: $m/z = 265$ (M^+).

2-Amino-3,5-dicyanopyridin-6-yl-(2-cyanomethylbenzothiazole) (**5e**; $C_{16}H_{18}N_6S$)

From **1e** and **2b**; yield: 78% (*DMF*/ethanol); m.p.: 242°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2200 (CN), 1620 (C=N) cm^{-1} ; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 pyr), 7.8 (brs, NH_2), 7.21–7.65 (m, 4H ar), 3.9 (s, CH–CN) ppm; MS: $m/z = 326$ (M^+).

2-Amino-3-benzoyl-5-cyano pyridin-6-yl-(2-cyanomethylbenzothiazole) (**5f**; $C_{22}H_{13}N_5OS$)

From **1f** and **2b**; yield: 75% (*DMF*/ethanol); m.p.: 190°C; IR (KBr): $\bar{\nu} =$3450 (NH_2), 2210 (CN), 1618 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.1 (s, H_4 pyr), 7.6 (brs, NH_2), 7.5–7.73 (m, 9H ar), 3.9 (s, CH–CN) ppm; MS: $m/z = 395$ (M^+).

2-Amino-3-carbethoxy-5-cyanopyridin-6-yl-(2-cyanomethylbenzothiazole) (**5g**; $C_{18}H_{13}N_5O_2S$)

From **1g** and **2b**; yield: 77% (*DMF*/ethanol); m.p.: 160°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2202 (CN), 1630 (COOEt), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 pyr), 7.8 (brs, NH_2), 7.3–7.65 (m, 4H ar), 4.3–3.5 (s, CH–CN), 1.3 (t, 3H, CH_3) ppm; MS: $m/z = 363$ (M^+).

2-Amino-3-thioacetamido-5-cyanopyridin-6-yl-(2-cyanomethylbenzothiazole) (**5h**; $C_{16}H_{10}N_6S_2$)

From **1h** and **2b**; yield: 73% (*DMF*/ethanol); m.p.: 220°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2204 (CN), 1629 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 pyr), 7.3–7.56 (m, 4H ar), 6.8 (brs, NH_2), 6.5 (brs, $CSNH_2$), 3.5 (s, CH–CN) ppm; MS: $m/z = 350$ (M^+).

2-Amino-3-acetamido-5-cyanopyridin-6-yl-(2-cyanomethylbenzothiazole) (**5i**; $C_{16}H_{10}N_6OS$)

From **1i** and **2b**; yield: 72% (*DMF*/ethanol); m.p.: 233°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2206 (CN), 1629 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 pyr), 7.15–7.54 (m, 4H ar), 6.8 (brs, NH_2), 6.3 (brs, $CONH_2$), 3.5 (s, CH–CN) ppm; MS: $m/z = 334$ (M^+).

2-Amino-3-benzothiazolyl-5-cyanopyridin-6-yl-(2-cyanomethylbenzothiazole) (**5j**; $C_{22}H_{12}N_6S_2$)

From **1j** and **2b**; yield: 75% (*DMF*/ethanol); m.p.: 180°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2204 (CN), 1630 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.2 (s, H_4 pyr), 7.21–7.63 (m, 8H ar), 6.8 (brs, NH_2), 3.6 (s, CH–CN) ppm; Ms: $m/z = 424$ (M^+).

2-Amino-3-benzoimidazolyl-5-cyanopyridin-6-yl-(cyanomethylbenzothiazole) (**5k**; $C_{22}H_{13}N_7S$)

From **1k** and **2b**; yield: 74% (*DMF*/ethanol); m.p.: 260°C; IR (KBr): $\bar{\nu} = 3450$ (NH_2), 2204 (CN), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, δ, 200 MHz): 8.7 (s, NH), 8.1 (s, H_4 pyr), 7.2–7.64 (m, 8H ar), 6.7 (brs, NH_2), 3.5 (s, CH–CN) ppm; MS: $m/z = 407$ (M^+).

General procedure for the synthesis of 2-amino-3,5-dicyano derivatives of pyridine (**9**)

Equimolar amounts of enaminonitrile **2b** (4 mmol) and **6** (4 mmol) in 25 cm^3 ethanol were treated with a few drops of *TEA*. The reaction mixture was refluxed for 3 h and the solid product was recrystallized from the solvent given below.

2-Amino-3,5-dicyano-4-phenylpyridin-6-yl-(2-cyanomethylbenzothiazole) (**9a**; $C_{22}H_{12}N_6S$)

From **6a** and **2b**; yield: 71% (*DMF*/ethanol); m.p.: 200°C; IR (KBr): $\bar{\nu}$ =3450 (NH_2), 2204 (CN), 1617 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 7.3–7.76 (m, 9H ar), 6.7 (brs, NH_2), 3.5 (s, CH–CN) ppm; MS: $m/z = 392$ (M^+).

2-Amino-3,5-dicyano-4-(o-tolyl)-pyridin-6-yl-(2-cyanomethylbenzothiazole) (**9b**; $C_{23}H_{14}N_6S$)

From **6b** and **2b**; yield: 75% (*DMF*/ethanol); m.p.: 240°C; IR (KBr): $\bar{\nu}$ = 3450 (NH_2), 2204 (CN), 1628 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 7.18–7.62 (m, 8H ar), 6.8 (brs, NH_2), 3.5 (s, CH–CN), 2.33 (s, CH_3) ppm; MS: $m/z = 406$ (M^+).

2-Amino-3,5-dicyano-4-(p-nitrobenzene)-pyridin-6-yl-(2-cyanomethylbenzothiazole) (**9c**; $C_{22}H_7N_7O_2S$)

From **6c** and **2b**; yield: 78% (*DMF*/ethanol) m.p.: 212°C; IR (KBr): $\bar{\nu}$ = 3450 (NH_2), 2210 (CN), 1620 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 7.26–7.54 (m, 8H ar), 6.6 (brs, NH_2), 3.5 (s, CH–CN) ppm; MS: $m/z = 436$ (M^+).

2-Amino-3,5-dicyano-4-(2,3,4-trimethoxymethyl)-pyridin-6-yl-(2-cyanomethylbenzothiazole) (**9d**; $C_{25}H_{18}N_6O_3S$)

From **6d** and **2b**; yield: 76% (*DMF*/ethanol); m.p.: 170°C; IR (KBr): $\bar{\nu}$ = 3450 (NH_2), 2204 (CN), 1628 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 7.2–7.68 (m, 6H ar), 6.8 (brs, NH_2), 3.93 (s, OCH_3), 3.88 (s, OCH_3), 3.81 (s, OCH_3), 3.5 (s, CH–CN) ppm; MS: $m/z = 482$ (M^+).

2-Amino-3,5-dicyano-4-(pyrido)-pyridin-6-yl-(2-cyanomethylbenzothiazole) (**9e**; $C_{21}H_{11}N_7S$)

From **6e** and **2b**; yield: 73% (*DMF*/ethanol); m.p.: 230°C; IR (KBr): $\bar{\nu}$ = 3450 (NH_2), 2202 (CN), 1628 (C–N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 200 MHz): 7.21–7.72 (m, 8H ar), 6.8 (brs, NH_2), 3.5 (s, CH–CN) ppm; MS: $m/z = 393$ (M^+).

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