J. prakt. Chem. 338 (1996) 681–683

Journal für praktische Chemie
Chemiker-Zeitung

Das Reagenz • The Reagent

Acylated Cyanatoarenes – Reagents for Convenient Cyanations

K. Buttke, and H.-J. Niclas

Berlin, Institut für Angewandte Chemie Berlin-Adlershof e. V.

Received April 10th, 1996

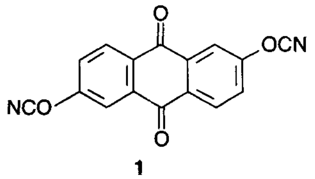
The electrophilic cyanation of carbanionic systems such as enamines and ketonenolates succeeds with various reagents, e.g. with cyanogen halides [1–4], arylcyanates [5–7], *p*-toluenesulfonyl cyanide [8], chlorosulfonylisocyanate [9, 10], Viehe's reagent [11], triphenylphosphine/thiocyanogen [12, 13], or cyanogen bromide/dimethylaminopyridine [14].

Thus, the pyrrolidine, piperidine and morpholine enamines of cyclic ketones have been treated with cyanogen halides in the presence of triethylamine to give the corresponding α-cyanoketones on hydrolysis [1–3]. Metallated dimethylhydrazones have been cyanated with BrCN leading to α-cyano dimethylhydrazones [4]. In some cases aryl cyanates have been used for introducing the cyano group into enamines and related compounds [5–7]. Phenyl cyanate and tosyl cyanide react with the anion generated by treatment of 1-(*N,N*-dimethylsulphamoyl)imidazoles with butyllithium to give the corresponding 2-cyanoimidazoles [7]. 2-Cyanoimidazoles have also been prepared using cyanogen bromide/dimethylaminopyridine [14]. Kinetic cyanation of ketone enolates with tosyl cyanide provides efficient routes to β-ketonitriles [8]. The cyanation of indoles and pyrroles succeeds with a combined reagent of triphenylphosphine and thiocyanogen [12, 13]. Finally, the electrophilic addition of chlorosulfonyl isocyanate to ketones or indoles affords the corresponding nitriles [9, 10]. 3-Cyanoindoles have also been prepared using Viehe's reagent [11]. Furthermore, the electrophilic cyanation of aromatics succeeds, e. g. with cyanogen halides [15, 16, 18, 19], cyanogen [18], trichloroacetonitrile [17–19], chlorosulfonyl isocyanate [20], arylcyanates [21] or tosyl cyanide [7]. Thus, the direct cyanation of reactive aromatic hydrocarbons in carbon disulfide using cyanogen bromide/aluminum chloride affords the appropriate nitriles after 18 hours at 48 °C in good yields [16]. The reaction of anilines, trichloroacetonitrile and BCl_3 in the presence of $SnCl_4$ or $AlCl_3$ gives 2-aminobenzonitriles [17]. Moreover, the treatment of phenols with CH_3SCN and $BCl_3/AlCl_3$ leads to 2-hydroxybenzonitriles [17]. A further method for introducing the cyano group into aromatics proceeds *via* chlorosulfonamides starting from chlorosulfonyl isocyanates [20]. Finally, electrophilic cyanation is performed with aryl cyanates. Thus, the nitrile group may be introduced into toluene or anisole by means of PhOCN with $AlCl_3$ + HCl as catalyst. The yields obtained are only moderate [5, 21, 22]. Despite the usefulness of the reagents mentioned above there are several factors limiting their general application, for example toxical or irritating activities, difficult accessibility, thermal instability, or small yields in some cases [12, 14].

Recently, we described the improved cyanation of aromatics, enamines and 1,3-dicarbonyl compounds using cyanatoarenes which are activated by carbonyl groups. We have found that cyanatoanthraquinone **1** and acylsubstituted cyanatobenzenes **2a, 2b** act as convenient and powerful reagents for the introduction of nitrile functions [23, 24]. The reagent of choice is determined by factors such as working-up procedures. Thus, the phenol formed from **2a** may be removed by distillation. The acylated cyanatoarenes **1, 2** are stable, easy to handle and simply accessible compounds. These reagents were prepared by modification of known procedures [21, 25, 26].

2,6-Dicyanatoanthraquinone (1)

0.01mol of the finely powdered 2,6-dihydroxyanthraquinone are thoroughly suspended in 80 ml of THF. Under stirring, cyanogen bromide (0.025 mol) is added in one portion at 0–10 °C. Over a period of 0.5h, triethylamine (0.02 mol) in



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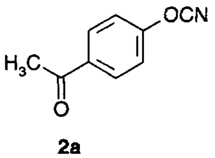
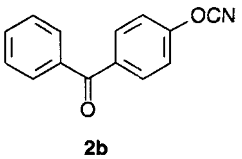


2a

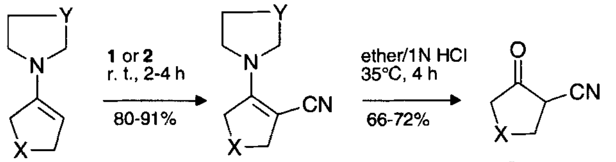


2b

*20 ml of THF is added. Stirring is continued for 30 min and the reaction mixture allowed to warm to room temperature. Then, 100 ml of water is added in order to dissolve the triethyl ammonium bromide formed. Compound **1** is isolated by suction, washed with water, and dried over $CaCl_2$. Yield: 84%, m. p. not detectable (cf. ref. [25]).*

Cyanation of Enamines

1 or **2** react with enamines at room temperature to give compounds **4** in excellent yields. Gentle isolation of **4** in high purity succeeds very easily using the cyanatoanthraquinone **1** followed by Kugelrohr distillation. The dihydroxyanthraquinone formed remains as residue and may be recovered. Compounds **4** may be transformed with hydrochloric acid into cyanoketones **5** in yields up to 72% [23].



3a-f **4a-f** **5a** X=CH_2 **5b** X=CH_2-CH_2

3,4	X	Y	Yield of **4** (%)
a	$-CH_2-$	$-CH_2-$	91
b	$-CH_2-CH_2$	$-CH_2-$	81
c	$-CH_2-$	$-CH_2-CH_2-$	80
d	$-CH_2-CH_2-$	$-CH_2-CH_2-$	82
e	$-CH_2-$	$-O-CH_2-$	89
f	$-CH_2-CH_2-$	$-O-CH_2-$	86

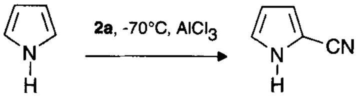
Cyanoenamines (**4**)

*A solution of **2a** (0.05 mol) in diethyl ether or THF (20 to 50 ml) is added under stirring at room temperature to a solution of the enamine **3** (0.05 mol) in 20 ml of diethyl ether. In the cases of **1** (only 0.025mol are necessary) and **2b** THF is used as solvent and the enamines are added to the suspension of cyanatoarenes. Stirring is continued for 2h, the solvent is evaporated, and the resulting oil is distilled using a Kugelrohr apparatus.*

*Cyanoketones **5** from Cyanoenamines* (**4**)

*A mixture of the appropriate cyanoenamine in diethyl ether (50 ml) and hydrochloric acid (1N, 60 ml) is stirred at 35–40 °C for 4h. The organic layer is separated and washed with a little water. Then the aqueous phase is adjusted to pH 6 and several times ectracted with diethyl ether. The combined ether phase is dried over Na_2SO_4 and fractionally distilled. Yields: **5a**: 72%, **5b**: 66%.*

2-Cyanopyrrole **6** is obtained by reaction of pyrrole with **1** at –70 °C in the presence of $AlCl_3$ as catalyst [23].



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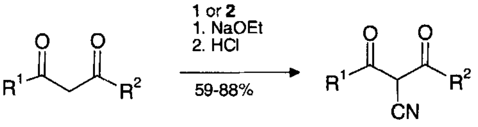
2-Cyanopyrrole (**6**)

*$AlCl_3$ (0.1 mol) is suspended in 50 ml of $CHCl_3$. To this suspension a solution of pyrrole (0.1 mol) in $CHCl_3$ (25 ml) is added at –70 °C. Then 0.1 mol of **2a** in $CHCl_3$ (50–100 ml) is added dropwise to the stirred suspension. After stirring at 0 °C for 6h, a stream of dry NH_3 is passed through until the mixture is basic. The precipitate is collected by suction and washed thoroughly with $CHCl_3$. The combined filtrate is washed several times with brine, dried over Na_2SO_4, and distilled. Yield: 50%, b.p. 115–120 °C/1.7 kpa.*

Cyanation of 1,3-Diketones

2-Cyano-1,3-diketones **7** are prepared when the sodium salts of 1,3-diketones are treated with compounds **2** under ice cooling [23].



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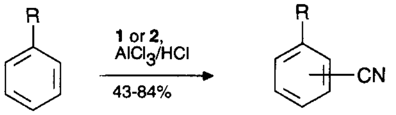
7	R^1	R^2	Yield (%)
a	CH_3	CH_3	62
b	C_6H_5	CH_3	59
c	C_6H_5	C_6H_5	88

2-Cyano-1,3-diketones **7**:

*0.05 mol of the diketone in diethyl ether (40 ml) are added under stirring and ice cooling to a solution of 0.05 mol sodium in absolute ethanol (20 ml). To this solution 0.05 mol of **2a** in THF (50 ml) are added dropwise under stirring for 1h. Then the ice-cooling is removed and stirring continued for 5h at room temperature. After standing overnight, the ether phase is reduced by evaporation, 150 ml of diethyl ether is added under stirring, the sodium salt obtained is isolated, and poured into ice/2N HCl. Then the precipitate is isolated by suction and recrystallized.*

Cyanation of Aromatics

The cyanation of alkyl- and alkoxy-substituted benzenes succeeds with improved *para*-selectivity when the cyanatoarenes **1** or **2** are used. The reaction is carried out with $AlCl_3$ + HCl as catalyst. Moderate to good yields of isolated carbonitriles **8** are obtained by treating the aromatic compounds with **1** or **2a** at 0 to 5°C [24].



8 R = OAlkyl, Alkyl

*4-Methoxybenzonitrile (**8**, R=OMe)*

*$AlCl_3$ (32.0 g, 0.24 mol) is added under ice-cooling and vigorous stirring to 100 ml of anisole. Then the mixture is added under stirring at –70 °C to a suspension of **1** (14.5 g, 0.05 mol) in 100 ml of carbon disulfide. The mixture is allowed*

to warm to 0 °C, and a stream of dry HCl is passed through until saturation is achieved. After standing overnight, the reaction mixture is diluted with 200 ml of diethyl ether, poured onto ice, filtered by suction, and the precipitate is washed with diethyl ether several times. The ether phase is then successively washed with 2N NaOH and water, dried over Na_2SO_4*, and distilled. Yield: 9.64 g (72%), b.p. 133–136 °C/ 16 Torr. Isomer distribution determined by GC: 100% of 4-methoxybenzonitrile.*

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Address for correspondence:
Prof. Dr. Hans–Joachim Niclas
Institut für Angewandte Chemie Berlin–Adlershof e.V.
Rudower Chaussee 5
D-12484 Berlin, Germany