2,4,4,6-Tetrabromocyclohexa-2,5-dienone in the presence of triphenylphosphine as a specific reagent for nucleophilic substitution in cyanohydrins

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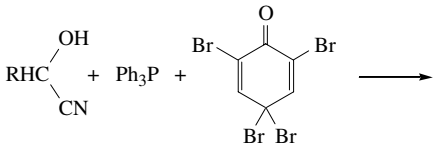
A convenient method for the synthesis of α-bromonitriles from aliphatic cyanohydrins using the 2,4,4,6-tetrabromocyclohexa-2,5-dienone complex with triphenylphosphine was developed.

Halonitriles can serve as starting materials for the synthesis of heterocyclic systems and biologically active compounds.[1,2] Published methods for the synthesis of halonitriles are based on radical processes often leading to mixtures of isomers.[3–5] The methods based on nucleophilic substitution for the hydroxyl group give low yields, or they are time-consuming multistage processes.[6,7]

Previously, we found that 2,4,4,6-tetrabromocyclohexa-2,5-dienone **1** in the presence of triphenylphosphine can be successfully used for the regio- and stereospecific substitution of bromine for hydroxyl in alcohols.[8] The above reagent can be employed for the nucleophilic substitution of bromine for hydroxyl in cyanohydrins in accordance with the following reaction scheme:



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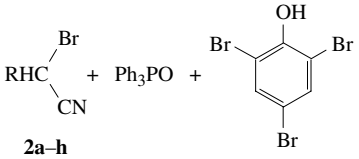


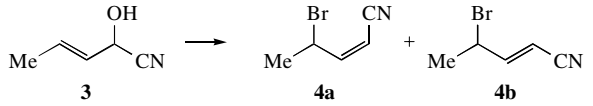
2a–h

It was found that an optimum ratio between the reagents (hydroxynitrile : tetrabromide **1** : triphenylphosphine) is 1:1.5:1.5. The substitution for aliphatic cyanohydrins occurs regiospecifically with the formation of the only product, α-bromonitrile, under mild conditions (0 °C, methylene chloride as a solvent).† The product structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy.‡ The times of the reactions, the yields of α-bromonitriles and some constants of the products are presented in Table 1.

It follows from the above data that an increase of steric hindrances at the α-carbon atom of cyanohydrins increases the reaction time, but it has no influence on the yield of α-bromonitriles.

Under similar conditions, the cyanohydrins of aromatic aldehydes also interact with the complex of triphenylphosphine and bromide **1** to form corresponding α-bromoarylacetonitriles (Table 1).† In this case, the substitution reaction fully occurs only for 24 h at room temperature. The yields of the products depend on substituents in a benzene ring.

Substitution for the hydroxyl group in α,β-conjugated hydroxynitriles is accompanied by allylic isomerisation. The reaction of crotonic aldehyde cyanohydrin **3** occurs under mild conditions at 5 °C in an inert atmosphere and completes in 1.5 h leading to 4-bromopentene-2-nitrile with 82% yield. Analysis of the ^{1}H and ^{13}C NMR spectra§ shows that the reaction product is a mixture of *cis*-**4a** and *trans*-**4b** isomers in a 1:1 ratio (determined by GLC).



3 **4a** **4b**

The ^{1}H NMR spectra exhibited the signals of the vinyl protons of 4-bromopentene-2-nitrile with the constant of spin–spin interaction J 10.81 Hz corresponding to a *cis*-configuration and the signals with the constant J 16.21 Hz corresponding to a *trans*-configuration (the ratio between the integrated intensities of *cis*:*trans* protons is 1:1). The ^{13}C NMR signals with chemical shifts of 153 and 100 ppm correspond to the carbon atoms of a double bond conjugated with the cyano group instead of the

Table 1 Reaction times and yields of α-bromonitriles.

Compound	R	Time/h	Yields of α-bromonitriles (%)	bp/°C (Torr)	Reference
2a	Me	1	55	52 (60)	9
2b	Et	1	60	60 (27)	10
2c	Pr^i	3	45	64 (20)	11
2c	Pr^i	24	65	64 (20)	11
2d	Pr	2	65	64 (11)	12
2e	Ph	24	60	oil	
2f	3-$NO_2C_6H_4$	24	70	mp 162	
2g	4-BrC_6H_4	24	90	mp 79–80	
2h	4-$Me_2NC_6H_4$	24	45	oil	

† *Synthesis of 2-alkylnitriles*: 6.15 g (15 mmol) of compound **1** in 5 ml of dichloromethane were added to 3.93 g (15 mmol) of PPh_3 on cooling in an inert atmosphere. After 10 min, 1 mmol of 2-hydroxyalkylnitrile was added. At the end of reaction, the solvent was evaporated and the residue was distilled.

Synthesis of 2-arylnitriles: 6.15 g (15 mmol) of compound **1** in 5 ml of dichloromethane were added to 3.93 g (15 mmol) of PPh_3 on cooling in an inert atmosphere. After 10 min, 1 mmol of 2-hydroxyarylnitrile was added. At the end of reaction, the solvent was evaporated and the residue was purified by column chromatography.

‡ *Selected spectral data.*

For **2a**: ^{1}H NMR (400 MHz, CDCl3) δ: 1.9 (d, 3H, Me), 4.3 (q, 1H, CH). ^{13}C NMR, δ: 20.93 (Me), 23.84 (CH), 118.03 (CN).

For **2b**: ^{1}H NMR, δ: 1.1 (t, 3H, Me), 2.1 (dt, 2H, CH_2), 4.3 (t, 1H, CH). ^{13}C NMR, δ: 11.28 (Me), 28.84 (CH_2), 30.05 (CH), 117.10 (CN).

For **2c**: ^{1}H NMR, δ: 1.15 (dd, 6H, 2Me), 2.2 (m, 1H, CH), 4.25 (d, 1H, CHBr). ^{13}C NMR, δ: 18.95 (Me), 19.45 (CH), 35.61 (CHBr), 116.42 (CN).

For **2d**: ^{1}H NMR, δ: 1.0 (t, 3H, Me), 1.6 (dq, 2H, MeCH_2), 2.1 (m, 2H, CH_2), 4.3 (t, 1H, CHCN). ^{13}C NMR, δ: 12.76 (Me), 20.19 (CH_2), 26.85 (CH_2), 38.18 (CH), 117.31 (CN).

For **2f**: ^{1}H NMR, δ: 6.95 (s, 1H, CH), 7.08 (m, 3H, Ar), 7.8 (m, 1H, Ar).

For **2g**: ^{1}H NMR, δ: 5.4 (s, 1H, CH), 7.39, 7.42, 7.46, 7.49 (Ar). ^{13}C NMR, δ: 26.56 (CH), 115.79 (CN), 124.77, 129.28, 132.47, 132.74 (Ar).

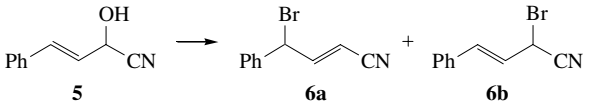
For **2h**: ^{1}H NMR, δ: 2.91 (s, 1H, CH), 3.14 (s, 6H, 2Me), 6.68 (d, 2H, Ar), 7.95 (d, 2H, Ar).

§ For **4a**: ^{1}H NMR ($CDCl_3$) δ: 1.84 (d, 3H, Me, ^3J 6.67 Hz), 5.02 (m, 1H, H^2, $^3J_{H^2,H^3}$ 10.81 Hz, ^3J 6.67 Hz, $^4J_{H^2,H^4}$ 0.56 Hz), 5.29 (dd, 1H, H^4, $^3J_{H^3,H^4}$ 10.81 Hz, $^4J_{H^4,H^2}$ 0.56 Hz), 6.60 (t, 1H, H^3, $^3J_{H^3,H^2} = {}^3J_{H^3,H^4}$ 10.81 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.99 (C^1), 42.39 (C^2), 98.54 (C^3), 153.20 (C^4), 114.31 (C^5).

For **4b**: ^{1}H NMR ($CDCl_3$) δ: 1.83 (d, 3H, Me, ^3J 6.78 Hz), 4.65 (m, 1H, H^2, $^3J_{H^2,H^3}$ 7.70 Hz, $^4J_{H^2,H^4}$ 1.15 Hz), 6.80 (dd, 1H, H^3, $^3J_{H^3,H^4}$ 16.21 Hz, $^3J_{H^3,H^2}$ 7.81 Hz), 5.54 (dd, 1H, H^4, $^3J_{H^4,H^3}$ 16.21 Hz, $^4J_{H^4,H^2}$ 1.15 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.10 (C^1), 43.84 (C^2), 100.27 (C^3), 153.69 (C^4), 116.14 (C^5).

signals with chemical shifts of 123 and 137 ppm corresponding to the carbon atoms of an isolated double bond. This fact also suggests that the allyllic rearrangement takes place.

Analogously, the nucleophilic substitution for hydroxyl in cyanohydrins of cinnamic aldehyde **5** results in a mixture of rearranged 4-bromo-4-phenylbutene-2-nitrile **6a** and 2-bromo-4-phenylbutene-3-nitrile **6b** in a 1:3 ratio. Both isomers were separated and identified by ^{1}H and ^{13}C NMR spectra. The value *J* 15.9 Hz for olefin protons gives evidence for a *trans*-configuration in both cases.



5 **6a** **6b**

The structure of bromonitrile **6a** was determined by ^{13}C NMR spectroscopy.¶ The chemical shifts of carbon atoms of the double bond conjugated with cyano group are 101.95 and 151.52 ppm similarly to 4-bromopentene-2-nitrile **4a**. In bromonitrile **6a**, the chemical shifts of the protons of the double bond are 5.53 and 7.01 ppm. For isomeric compound **6b**, the chemical shifts of carbon atoms of the double bond are 125.06 and 133.18 ppm; the signals of vinyl protons are at 5.83 and 6.81 ppm.¶ Thus, in cinnamic aldehyde, the allylic isomerisation occurs only by 25%.

¶ For **6a**: ^{1}H NMR, δ: 5.53 (dd, 1H, CH, *J* 16 Hz), 5.61 (dd, 1H, CHBr), 7.01 (dd, 1H, CH, *J* 16 Hz), 7.4 (m, 5H, Ar). ^{13}C NMR, δ: 49.99 (CHBr), 101.96 (CH), 151.52 (CH), 116.12 (CN), 126.61, 127.06, 128.89, 129.00 (Ar).

For **6b**: ^{1}H NMR, δ: 5.35 (dd, 1H, CHBr), 5.83 (dd, 1H, CH, *J* 16.2 Hz), 6.81 (dd, 1H, CH, *J* 16.2 Hz), 7.5 (m, 5H, Ar). ^{13}C NMR, δ: 29.67 (CHBr), 125.06 (CH), 133.18 (CH), 117.38 (CN), 127.48, 127.83, 129.22, 129.43 (Ar).

Thus, we developed a convenient method for the synthesis of aliphatic α-bromonitriles using a new reagent – the complex of 2,4,4,6-tetrabromocyclohexa-2,5-dienone with triphenylphosphine.

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