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SYNTHESIS OF SPIRO[ISOQUINOLINE-4,4'-PYRAN]-3-IMINES

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A method has been developed for the synthesis of 4-[2-(bromomethyl)phenyl]tetrahydro-2H-4-pyrancarbonitrile and a study was carried out on the reaction of this compound with primary amines, which, depending on the conditions, leads to either 4-[2-(R-aminomethyl)phenyl]tetrahydro-2H-4-pyrancarbonitriles or hydrobromides of 2-R-aryl-2,3,2',3',5',6'-hexahydrospiro[isoquinoline-4(1H),4'-pyran]-3-imines.

Keywords: heterocyclic spirans, spirocyclic isoquinolines, spiro[isoquinolinepyrans].

Spiro[isoquinoline-4,4'-pyrans] hold interest as potential biologically active compounds since useful properties have been found for a series of these compounds [1-4]. On the other hand, the number of methods for the synthesis of such compounds is limited [3, 5, 6]. Hence, it would be helpful to find intermediates, which could be used to synthesize new spiro[isoquinoline-4,4'-pyrans]. We have already shown that 2-(bromomethyl)phenylacetonitrile (**1**) is a promising intermediate for the synthesis of new functional derivatives of heterocyclic systems, including systems previously not reported in the literature [7-10]. In the present work, we attempted to modify the structure of bromonitrile **1** by placing the methylene group of the cyanomethyl fragment into the polymethylene chain of a hydrogenated pyran ring. The synthesis of such an intermediate involved the cycloalkylation of *o*-methylphenylacetonitrile (**2**) using 2,2'-β,β'-dichlorodiethyl ether (**3**) with subsequent bromination of the resultant 4-(2-methylphenyl)tetrahydro-2H-4-pyrancarbonitrile (**4**) obtained by cycloalkylation at the methyl group. Analysis of the literature data showed that such transformations have not been reported. According to Arseniadis et al. [11], the cycloalkylation of phenylacetonitriles using α,ω-dihalides most often is carried out under phase transfer catalysis conditions employing concentrated alkali solutions or strong bases as sodium hydride, sodium amide, and lithium diisopropylamide in aprotic solvents. Since the former method is attractive in light of the availability of the base and simplicity of the reaction, we first studied the possibility of synthesizing tetrahydropyan **4** under these conditions. However, all our attempts were unsuccessful. Thus, only the starting reagents were recovered from the reaction mixture by extraction and subsequent fractionation using tetrabutylammonium chloride and tetraethylammonium chloride as the phase transfer catalysts despite using rather vigorous conditions (60-70°C, 30 h reaction time). The fraction collected at 140-175°C at 0.5 mm Hg using triethylbenzylammonium chloride and other conditions equal was a 1:4 mixture of the desired tetrahydropyran **4** and alkylated intermediate **5**. Analogously, a 1:5 mixture of **4** and **5** qualitatively determined by GC/MS was obtained using dibenzo[18]crown-6. The quantitative determination of the ratio of these products was carried out by ^{1}H NMR spectroscopy. Satisfactory results were obtained using sodium hydride as the base. This reaction may be carried out either in dimethylsulfoxide or, preferably, toluene. However, the yield of **4** does not exceed 40% in either case. Further bromination of pyran **4** by N-bromosuccinimide in carbon tetrachloride gave the desired product, 4-[2-bromomethyl)phenyl]tetrahydropyran-2H-4-carbonitrile (**6**) in high yield.

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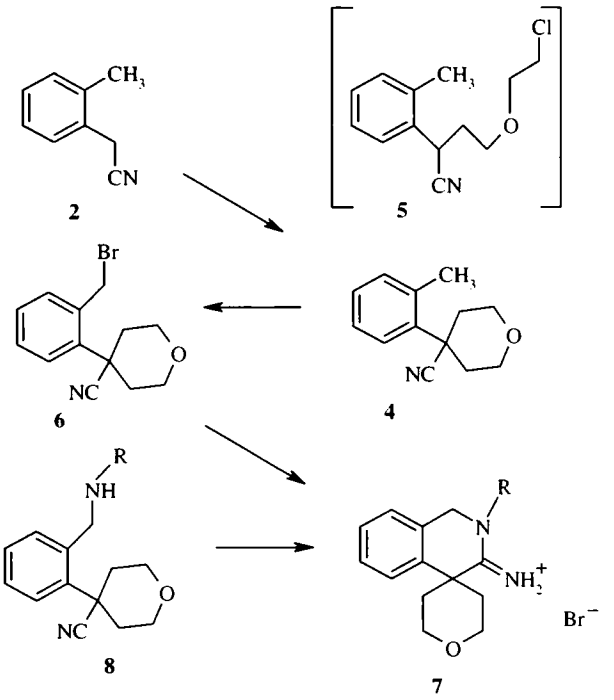

7,8 a R = C_6H_5; **c** $C_6H_4CH_3$-*p*; **k** $CH_2C_6H_5$; **7 b** R = $C_6H_4OCH_3$-*p*;
d R= $C_6H_4CH_3$-*o*; **e** R = C_6H_4Cl-*m*; **f** R = C_6H_4Cl-*o*; **g** R = C_6H_4Br-*p*; **h** R = $C_6H_4COCH_3$-*p*;
i R = $C_6H_4NO_2$-*p*; **j** R = $C_6H_4NO_2$-*m*; **l** R = $(CH_2)_4CH_3$

The reaction of bromonitrile **1** with aliphatic amines and arylamines bearing electron-donor substituents in the aromatic ring leads to N-alkyl- and N-aryl-2-(aminomethyl)phenylacetonitriles [7]. Thus, we might have expected that such products would also be formed in the case of bromonitrile **6**. However, the reaction of **6** with aromatic amines leads, independently of the substituent in the aryl ring, to hydrobromides of 2-aryl-2,3,2',3',5',6'-hexahydrospiro[isoquinoline-4(1H),4'-pyran]-3-imines **7** with spectral characteristics similar to those of hydrobromides of 2-R-1,2,3,4-tetrahydroisoquinoline-3-imines [7]. Thus, the IR spectra lack a nitrile group stretching band but have strong C=N bands at 1645-1650 cm^{-1} and broad bands with several maxima at 3000-3380 cm^{-1} for the N–H group (see Table 1). Broad signals for the iminium group as two one-proton singlets or one two-proton singlets are seen in the downfield part of their ^1H NMR spectra taken in DMSO-d_6, which disappear in the presence of D_2O. The signals for protons at $C_{(1)}$ were observed as singlet at 5.05-5.20 ppm. Exceptions are found when a substituent is present in the *o*-position of the 1-aryl group. The protons of this methylene group in compounds **7d** and **7f** give two doublets with 18 Hz geminal coupling constant. The lack of magnetic equivalence in this proton pair is a consequence of steric hindrance to free rotation about the $N_{(2)}$–$C_{(Ar)}$ bond of the 2-aryl group extruded from the plane of the isoquinoline ring system [10].

The reaction of bromonitrile 6 with more basic benzylamine and *n*-amylamine leads, as indicated by IR and ^1H NMR spectroscopy, to mixtures of the hydrobromides of the corresponding aminonitriles **8** formed in the first step and the products of their cyclization **7**. Heating these mixtures in acetic acid solution in the presence of hydrogen bromide gives pure salts of isoquinolinimines **7k** and **7l**. The highly basic amines apparently compete with sterically hindered amines **8** for HBr, thereby suppressing the acid-catalyzed intramolecular interaction of the nitrile and amino groups in **8**. Thus, we might expect that the reaction of bromonitrile **6** with amines in the presence of additional bases would stop at the formation of aminonitriles **8**. In fact, while salts **7** are formed upon heating solutions of these mixtures in 2-propanol acidified with HBr, the reaction between bromonitrile **6** and benzylamine in the presence of potassium carbonate as the additional base leads to 4-[2-(benzylaminomethyl)-phenyl]tetrahydro-2H-pyran-4-carbonitrile **8k**, which, upon heating in the presence of HBr undergoes cyclization

TABLE 1. Constants and Spectral Characteristics of Spiro[isoquinoline-4,4'-pyran]-3-imines

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	IR spectra, cm^{-1}			^1H NMR spectra, δ, ppm*					Yield, %
		N	Hal		N'–H	C=N	other bands	$O(CH_2)_2$, m, 4H	$C(CH_2)_2$ m, 4H	NCH_2 s, 2H	$N'H_2$	other signals	
1	2	3	4	5	6	7	8	9	10	11	12	13	14
7a	$C_{19}H_{20}N_2O \cdot HBr$	7.40 / 7.50	21.25 / 21.40	247	3025 3380	1630		3.80	2.30	5.11	9.04 8.71		62
7b	$C_{20}H_{22}N_2O_2 \cdot HBr$	7.17 / 6.95	19.96 / 19.81	167.5	3120 3400	1655		4.33	2.64	5.10	—	4.02 (3H, s, OCH_3)	63
7c	$C_{20}H_{22}N_2O \cdot HBr$	7.31 / 7.23	20.87 / 20.63	239	3065 3080	1645		4.34	2.63	5.10	—	2.49 (3H, s, OCH_3)	57
7d	$C_{20}H_{22}N_2O \cdot HBr$	7.31 / 7.23	20.64 / 20.63	234	3100 3395	1655		4.32	2.62	5.18*2 4.97*2	—	2.40 (3H, s, OCH_3)	47
7e	$C_{19}H_{19}ClN_2O \cdot HBr$	6.94 / 6.87	28.54 / 28.30	169.5	3090 3300	1655		3.82	2.29	5.12	9.10 8.88		70
7f	$C_{19}H_{19}ClN_2O \cdot HBr$	6.97 / 6.88	28.52 / 28.30	242	3080 3360	1670		4.30	2.66	5.29*2 4.91*2	—		75

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
7g	$C_{19}H_{19}BrN_2O \cdot HBr$	6.25 6.19	35.39 35.34	276	3060 3380	1640		3.82	2.29	5.10	9.09 8.83		65
7h	$C_{21}H_{22}N_2O_2 \cdot HBr$	6.80 6.74	19.40 19.24	225	2980 3215	1665	1675 (C=O)	3.84	2.30	5.14	8.96	2.66 (3H, s, $COCH_3$)	65
7i	$C_{19}H_{19}N_3O_3 \cdot HBr$	10.22 10.05	19.31 19.10	283	3075 3340	1655	1350 1520 (NO_2)	3.82	2.32	5.10	9.12		50
7j	$C_{19}H_{19}N_3O_3 \cdot HBr$	10.12 10.05	19.46 19.10	247	3080 3420	1645	1350 1520 (NO_2)	3.83	2.23	5.20	9.09		68
7k	$C_{20}H_{22}N_2O \cdot HBr$	7.13 7.23	20.90 20.63	262	3090 3260	1660		3.74	2.22	5.02	9.41 9.04	4.84 (2H, s, CH_2Ph)	72
7l	$C_{18}H_{26}N_2O \cdot HBr$	7.67 7.63	21.73 21.75	212	3040 3240	1655		3.73	2.18	4.92	9.12 8.82	0.88 (3H, t, CH_3); 1.34 (4H, m, $(CH_2)_2CH_3$); 1.59 (2H, m, $NCH_2C\underline{H}_2$); 3.95*[3] (2H, m, $NC\underline{H}_2CH_2$)	60

* The spectra of **7b-f** were taken in deuterotrifluoroacetic acid and the others were taken in DMSO-d_6. The description of the aromatic proton multiplets is omitted.

*[2] One-proton doublets, coupling constant 18 Hz.

*[3] Partially overlapped by multiplet at 3.73 ppm for the $O(CH_2)_2$ protons.

to the corresponding salt **7k**. In the case of the reaction of bromonitrile **6** with aniline and toluidine, we showed that the reaction with arylamines may be stopped at the formation of aminonitriles **8** by carrying out the reaction in the presence of sodium acetate. The structure of aminonitriles **8** was indicated by their IR spectra, which showed N–H and C≡N bands. Furthermore, the proton of the secondary amino group in the ^{1}H NMR spectra appears as a broad triplet with coupling constant of 5 Hz, while the protons of the adjacent methylene group appear as a doublet with the same constant. In the presence of D_2O, the amino group signal disappears and the methylene group doublet is converted into a singlet. Aminonitriles **8** are very stable compounds. However, heating these derivatives in acetic acid solution in the presence of excess HBr leads to their ready conversion to cyclic salts **7**.

EXPERIMENTAL

The IR spectra were taken for KBr pellets on a Pye Unicam SP3-300 spectrometer. The ^{1}H NMR spectra were recorded for solutions in DMSO-d_6 on a Bruker WP-100SY spectrometer with TMS as the internal standard. Salts **7i,h** were crystallized from methanol, **7k** was recrystallized from acetic acid–acetonitrile, and the other products were recrystallized from 2-propanol. The characteristics of these compounds are given in Table 1.

4-(2-Methylphenyl)tetrahydro-4-pyrancarbonitrile (4). A flask was treated to remove moisture and anhydrous toluene (50 ml) and 80% sodium hydride emulsion in vaseline (10 g, 0.33 mol) were added. A mixture of nitrile **2** (18.5 ml, 0.15 mol) and β,β'-dichlorodiethyl ether **3** (17.6 ml, 0.15 mol) were added slowly with stirring and ice cooling. Stirring was continued until hydrogen was no longer released (3-4 h) and then excess sodium hydride was decomposed by adding 2-propanol (10 ml). A sample of water (100 ml) was added to the mixture and the toluene layer was separated. The aqueous layer was extracted with toluene. The combined toluene extracts were dried over Na_2SO_4. The solvent was distilled off at reduced pressure. The residue was distilled in vacuum, taking the fraction distilling at 150-160°C (0.5 mm Hg). The oily product readily gives colorless crystals. Yield of nitrile **4** 11.8 g (39%); mp 80°C (2-propanol–hexane, 1:3). IR spectrum: 2240 (C≡N), 2860, 2930, 2960 cm^{-1} (CH). ^{1}H NMR spectrum ($CDCl_3$): 1.9-2.4 (4H, m, 2-, 6-H); 2.65 (3H, s, CH_3); 3.8-4.2 (4H, m, 3-, 5-H); 7.26 ppm (4H, s, H arom). Found, %: C 77.45; H 7.35; N 6.92. $C_{13}H_{15}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

4-[2-(Bromomethyl)phenyl]tetrahydropyran-4-carbonitrile (5). A sample of N-bromosuccinimide (9.8 g, 0.55 mol) and azodiisobutyronitrile (100 mg) were added to a solution of **4** (10.1 g, 0.05 mol) in CCl_4 (100 ml). The mixture was heated at reflux with stirring for 14 h, cooled, and filtered. The filtrate was evaporated at reduced pressure and the residue was triturated with hexane. The solid was filtered off and washed with hexane to give 12.7 g (91%) of colorless crystalline **5**; mp 94°C (2-propanol). IR spectrum: 2240 (C≡N), 2860, 2930, 2960 cm^{-1} (CH). ^{1}H NMR spectrum ($CDCl_3$): 1.9-2.5 (4H, m, 2-, 6-H); 3.85-4.25 (4H, m, 3-, 5-H); 4.91 (2H, s, CH_2–Br); 7.2-7.7 ppm (4H, s, H arom). Found, %: Br 28.66; N 4.98. $C_{13}H_{14}BrNO$. Calculated, %: Br 28.52; N 5.00.

Hydrobromides of 2-Aryl-2,3,2',3',5',6'-hexahydrospiro[isoquinoline-4(1H),4'-pyran]-3-imines (7a-j). A mixture of bromonitrile **6** (0.84 g, 3 mmol) and arylamine (3 mmol) in 2-propanol (10 ml) was heated at reflux for 8 h and cooled. The crystalline precipitate was filtered off and washed with 2-propanol. The products thereby obtained by reaction between bromonitrile **6** and benzylamine or *n*-amylamine are mixtures of hydrobromides of the corresponding aminonitriles **8** and the products of their cyclization **7k,l**. In order to complete the cyclization, the mixture obtained was dissolved in a minimal amount of acetic acid and heated at reflux in the presence of hydrobromic acid (0.5 ml) for 3 h. The crystalline product obtained upon filtration of the cooled reaction mixture is the corresponding individual salt **7k,l**.

4-[2-(Benzylaminomethyl)phenyl]tetrahydro-4-pyrancarbonitrile (8). A mixture of bromonitrile **6** (0.84 g, 3 mmol), freshly roasted potassium carbonate (1.7 g, 12 mmol), and benzylamine (0.33 ml, 3 mmol) in 2-propanol (10 ml) was heated at reflux for 2 h. The mixture was filtered hot. The precipitate formed in the cooled filtrate was filtered off. Yield of nitrile **8** 0.5 g (43%); mp 105-106°C (2-propanol). IR spectrum: 2240 (C≡N), 3320 cm^{-1} (NH). ^{1}H NMR spectrum (DMSO-d_6): 1.8-2.4 (4H, m, 2-, 6-H); 3.4-4.1 (8H, overlapping m, 3-, 5-H, and two s $C\underline{H}_2NHC\underline{H}_2$); 7.2-7.8 ppm (9H, m, H arom). Found, %: C 78.53; H 7.15; N 9.02. $C_{20}H_{22}N_2O$. Calculated, %: C 78.40; H 7.24; N 9.14.

4-[2-(Phenylaminomethyl)phenyl]tetrahydro-4-pyrancarbonitrile (8a) was obtained analogously using sodium acetate in four-fold excess as the base. Yield of aminonitrile **8a** 62%; mp 147-148°C (2-propanol). IR spectrum: 2240 (C≡N), 3400 cm^{-1} (NH). ^1H NMR spectrum in DMSO-d_6: 1.9-2.4 (4H, m, 2-, 6-H); 3.6-4.1 (4H, m, 3-, 5-H); 4.58 (2H, d, J = 5 Hz, NHC$\underline{H}_2$); 6.18 (1H, br. t, J = 5 Hz, N$\underline{H}$CH$_2$); 6.5-6.7 (3H, m); 7.08 (2H, t, J = 8 Hz); 7.3-7.7 ppm (4H, m, H arom). Found, %: C 78.23; H 6.99; N 9.46. $C_{19}H_{20}N_2O$. Calculated, %: C 78.05; H 6.90; N 9.58.

4-[2-(*p*-Tolylaminomethyl)phenyl]tetrahydro-4-pyrancarbonitrile (8c) was synthesized analogously to **8a** in 55% yield; mp 160-161°C (2-propanol). IR spectrum: 2240 (C≡N), 3400 cm^{-1} (NH). ^1H NMR spectrum in DMSO-d_6: 1.9-2.4 (4H, m, 2-, 6-H), 2.13 (3H, s, superposed on multiplet at 1.9-2.4, CH_3); 3.6-4.1 (4H, m, 3-, 5-H); 4.54 (2H, d, J = 5 Hz, NHC$\underline{H}_2$); 5.91 (1H, br. t, J = 5 Hz, N$\underline{H}$CH$_2$); 6.52 (2H, d, J = 8 Hz, 2-H, 6-H toluidine); 6.88 (2H, d, J = 8 Hz, 3-, 5-H toluidine); 7.3-7.8 ppm (4H, m, H arom). Found, %: C 78.29; H 7.33; N 9.19. $C_{20}H_{22}N_2O$. Calculated, %: C 78.40; H 7.24; N 9.14.

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