

Ring Transformations of Heterocyclic Compounds. IX [1].
 Trifluoromethyl Substituted 2-Amino-3,4,6-triarylbenzophenones
 by Ring Transformation of 2,4,6-Triarylpyrylium Salts
 with Trifluoromethylbenzyl Cyanides

Thomas Zimmermann

Wissenschaftler-Integrations-Programm, Koordinierungs- und Aufbau-Initiative für die Forschung in den neuen
 Bundesländern e.V., Permoserstraße 15, D-04303 Leipzig, Germany

Received November 22, 1993

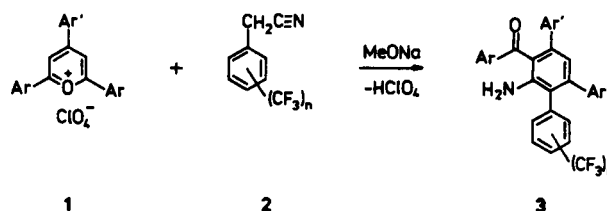
The preparation of hitherto unknown trifluoromethyl substituted 2-amino-3,4,6-triarylbenzophenones **3** by a 2,5-[C₄+C₂] ring transformation of 2,4,6-triarylpyrylium salts **1** with trifluoromethylbenzyl cyanides **2** in the presence of sodium methanolate in methanol is reported. Spectroscopic data of the benzophenones **3** and the mode of their formation are discussed.

J. Heterocyclic Chem., **31**, 277 (1994).

2-Aminobenzophenones represent valuable starting materials for the synthesis of a wide variety of heterocyclic systems [2]. Furthermore, 2-aminobenzophenones and heterocycles derived from them possess important pharmacological properties and have found clinical utility [2]. Recently we reported an efficient synthesis of 2-aminobenzophenones which starts from 2,4,6-triarylpyrylium salts **1** [3] and 4-nitrobenzyl cyanide or pyridyl acetonitriles and gives by pyrylium ring transformation former unknown 3-(4-nitrophenyl) and 3-pyridyl derivatives, respectively [4,5]. These investigations and the importance of fluorine for the biological activity of organic compounds [6] prompted us to look for reactions which lead to fluorine containing 2-aminobenzophenones by ring transformation of pyrylium salts.

When the 2,4,6-Triarylpyrylium salts **1a-f** were treated with 2-(trifluoromethyl)benzyl cyanide (**2a**) in the presence of sodium methanolate in boiling methanol the 3-[2-(trifluoromethyl)phenyl] substituted 2-amino-4,6-diarylbenzophenones **3a-f** were obtained by pyrylium ring transformation. By the same type of reaction the 2-amino-4,6-diarylbenzophenones **3g-l** with a 4-(trifluoromethyl)phenyl substituent in position 3 can be synthesized from the salts **1a-f** and 4-(trifluoromethyl)benzyl cyanide (**2b**). Contrary to the 2- and 4-(trifluoromethyl)benzyl cyanides **2a,b** the 3-(trifluoromethyl) isomer and pyrylium salts **1** gave no ring transformation products. Here the introduction of a second *meta*-positioned trifluoromethyl group into the benzyl cyanide was necessary to enable a transformation. In this way from the salts **1a-h** and 3,5-bis(trifluoromethyl)benzyl cyanide (**2c**) the 2-amino-4,6-diaryl-3-[3,5-bis(trifluoromethyl)phenyl]benzophenones **3m-t** were prepared. The compounds obtained by these syntheses represent 2-aminobenzophenones with a new substitution pattern.

The structure of the 2-aminobenzophenones **3a-t** is in agreement with the results of the elemental analyses and the spectroscopic data (cf. Table 1 and Table 2). In the



1	2	Ar	Ar'	(CF ₃) _n	3
a	a	Ph	Ph	2-CF ₃	a
b	a	Ph	4-Me-C ₆ H ₄	2-CF ₃	b
c	a	Ph	4-MeO-C ₆ H ₄	2-CF ₃	c
d	a	Ph	4-Cl-C ₆ H ₄	2-CF ₃	d
e	a	Ph	4-Br-C ₆ H ₄	2-CF ₃	e
f	a	4-Me-C ₆ H ₄	Ph	2-CF ₃	f
a	b	Ph	Ph	4-CF ₃	g
b	b	Ph	4-Me-C ₆ H ₄	4-CF ₃	h
c	b	Ph	4-MeO-C ₆ H ₄	4-CF ₃	i
d	b	Ph	4-Cl-C ₆ H ₄	4-CF ₃	j
e	b	Ph	4-Br-C ₆ H ₄	4-CF ₃	k
f	b	4-Me-C ₆ H ₄	Ph	4-CF ₃	l
a	c	Ph	Ph	3,5-(CF ₃) ₂	m
b	c	Ph	4-Me-C ₆ H ₄	3,5-(CF ₃) ₂	n
c	c	Ph	4-MeO-C ₆ H ₄	3,5-(CF ₃) ₂	o
d	c	Ph	4-Cl-C ₆ H ₄	3,5-(CF ₃) ₂	p
e	c	Ph	4-Br-C ₆ H ₄	3,5-(CF ₃) ₂	q
f	c	4-Me-C ₆ H ₄	Ph	3,5-(CF ₃) ₂	r
g	c	4-Cl-C ₆ H ₄	Ph	3,5-(CF ₃) ₂	s
h	c	4-Br-C ₆ H ₄	Ph	3,5-(CF ₃) ₂	t

infrared spectra the presence of a primary amino group is documented by absorptions at 3468-3516 cm⁻¹ and at 3372-3412 cm⁻¹ (asymmetrical and symmetrical NH-vibration); the carbonyl group causes a C=O absorption at 1632-1657 cm⁻¹. A characteristic feature of the ¹H nmr spectra are the singlet of the protons of the amino group at

Table 1
Physical and Analytical Data for the 2-Aminobenzophenones 3a-t

No.	-benzophenone	Yield (%)	Mp (°C)	Molecular Formula (Molecular Weight)	Analysis (%)		
					Calcd./Found	C	H
3a	2-amino-4,6-diphenyl-3-[2-(trifluoromethyl)phenyl]-	43	213-215	C ₃₂ H ₂₂ F ₃ NO (493.5)	77.88	4.49	2.84
					77.94	4.41	2.89
3b	2-amino-6-(4-methylphenyl)-4-phenyl-3-[2-(trifluoromethyl)phenyl]-	71	166-168	C ₃₃ H ₂₄ F ₃ NO (507.6)	78.09	4.77	2.76
					78.21	4.69	2.73
3c	2-amino-6-(4-methoxyphenyl)-4-phenyl-3-[2-(trifluoromethyl)phenyl]-	62	152-153	C ₃₃ H ₂₄ F ₃ NO ₂ (523.6)	75.71	4.62	2.68
					75.68	4.70	2.63
3d	2-amino-6-(4-chlorophenyl)-4-phenyl-3-[2-(trifluoromethyl)phenyl]-	27	161-163	C ₃₂ H ₂₁ ClF ₃ NO (528.0)	72.80	4.01	2.65
					72.90	4.02	2.71
3e	2-amino-6-(4-bromophenyl)-4-phenyl-3-[2-(trifluoromethyl)phenyl]-	13	164-165	C ₃₂ H ₂₁ BrF ₃ NO (572.4)	67.14	3.70	2.45
					67.03	3.76	2.41
3f	2-amino-4'-methyl-4-(4-methylphenyl)-6-phenyl-3-[2-(trifluoromethyl)phenyl]-	59	221-223	C ₃₄ H ₂₆ F ₃ NO (521.6)	78.30	5.02	2.69
					78.19	5.10	2.69
3g	2-amino-4,6-diphenyl-3-[4-(trifluoromethyl)phenyl]-	61	243-244	C ₃₂ H ₂₂ F ₃ NO (493.5)	77.88	4.49	2.84
					77.81	4.41	2.86
3h	2-amino-6-(4-methylphenyl)-4-phenyl-3-[4-(trifluoromethyl)phenyl]-	80	242-243	C ₃₃ H ₂₄ F ₃ NO (507.6)	78.09	4.77	2.76
					78.20	4.71	2.80
3i	2-amino-6-(4-methoxyphenyl)-4-phenyl-3-[4-(trifluoromethyl)phenyl]-	87	242-244	C ₃₃ H ₂₄ F ₃ NO ₂ (523.6)	75.71	4.62	2.68
					75.78	4.69	2.70
3j	2-amino-6-(4-chlorophenyl)-4-phenyl-3-[4-(trifluoromethyl)phenyl]-	27	227-228	C ₃₂ H ₂₁ ClF ₃ NO (528.0)	72.80	4.01	2.65
					72.83	4.07	2.68
3k	2-amino-6-(4-bromophenyl)-4-phenyl-3-[4-(trifluoromethyl)phenyl]-	21	222-224	C ₃₂ H ₂₁ BrF ₃ NO (572.4)	67.14	3.70	2.45
					67.20	3.76	2.39
3l	2-amino-4'-methyl-4-(4-methylphenyl)-6-phenyl-3-[4-(trifluoromethyl)phenyl]-	81	225-226	C ₃₄ H ₂₆ F ₃ NO (521.6)	78.30	5.02	2.69
					78.20	5.04	2.68
3m	2-amino-4,6-diphenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	74	166-167	C ₃₃ H ₂₁ F ₆ NO (561.5)	70.59	3.77	2.49
					70.50	3.71	2.42
3n	2-amino-6-(4-methylphenyl)-4-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	89	153-154	C ₃₄ H ₂₃ F ₆ NO (575.6)	70.95	4.03	2.43
					70.88	4.01	2.48
3o	2-amino-6-(4-methoxyphenyl)-4-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	57	151-153	C ₃₄ H ₂₃ F ₆ NO ₂ (591.6)	69.03	3.92	2.37
					69.18	3.85	2.39
3p	2-amino-6-(4-chlorophenyl)-4-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	32	143-144	C ₃₃ H ₂₀ ClF ₆ NO (596.0)	66.51	3.38	2.35
					66.30	3.31	2.39
3q	2-amino-6-(4-bromophenyl)-4-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	60	156-158	C ₃₃ H ₂₀ BrF ₆ NO (640.4)	61.89	3.15	2.19
					61.93	3.11	2.24
3r	2-amino-4'-methyl-4-(4-methylphenyl)-6-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	45	132-134	C ₃₅ H ₂₅ F ₆ NO (589.6)	71.30	4.27	2.38
					71.36	4.29	2.39
3s	2-amino-4'-chloro-4-(4-chlorophenyl)-6-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	55	179-180	C ₃₃ H ₁₉ Cl ₂ F ₆ NO (630.4)	62.87	3.04	2.22
					62.92	3.10	2.30
3t	2-amino-4'-bromo-4-(4-bromophenyl)-6-phenyl-3-[3,5-bis(trifluoromethyl)phenyl]-	85	180-182	C ₃₃ H ₁₉ Br ₂ F ₆ NO (719.3)	55.10	2.66	1.95
					55.11	2.69	1.98

Table 2
Spectral Data for the 2-Aminobenzophenones **3a-t**

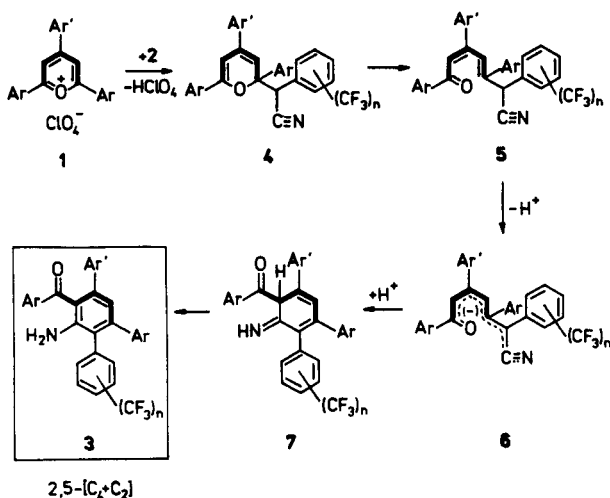
Compound	IR (KBr) (cm ⁻¹) NH, CO	UV (CH ₃ CN) λ_{\max} (nm) (log ϵ)	¹ H-NMR (DMSO-d ₆) [a] δ (ppm)
3a [b]	3488, 3392, 1656	242 (4.67), 292 sh (3.95), 372 (3.53)	4.44 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 7.04-7.65 (m, 19H, ArH)
3b	3488, 3388, 1654	244 (4.68), 294 sh (3.91), 370 sh (3.50)	2.08 (s, 3H, CH ₃), 4.36 (s, 2H, NH ₂), 6.64 (s, 1H, 5-H), 6.90-7.64 (m, 18H, ArH)
3c	3480, 3388, 1654	249 (4.66), 311 sh (3.88), 370 sh (3.59)	3.56 (s, 3H, OCH ₃), 4.37 (s, 2H, NH ₂), 6.64 (s, 1H, 5-H), 6.66-7.64 (m, 18H, ArH)
3d	3488, 3384, 1656	245 (4.70), 294 sh (3.95), 376 (3.55)	4.50 (s, 2H, NH ₂), 6.65 (s, 1H, 5-H), 7.08-7.65 (m, 18H, ArH)
3e	3488, 3392, 1657	246 (4.70), 294 sh (3.95), 377 (3.56)	4.49 (s, 2H, NH ₂), 6.64 (s, 1H, 5-H), 7.11-7.65 (m, 18H, ArH)
3f	3492, 3396, 1648	243 (4.65), 294 sh (4.06), 368 sh (3.53)	2.11 (s, 3H, CH ₃), 2.17 (s, 3H, CH ₃), 4.27 (s, 2H, NH ₂), 6.64 (s, 1H, 5-H), 6.87-7.65 (m, 17H, ArH)
3g [b]	3472, 3376, 1636	244 (4.66), 292 sh (3.98), 376 (3.55)	4.62 (s, 2H, NH ₂), 6.69 (s, 1H, 5-H), 7.03-7.61 (m, 19H, ArH)
3h	3468, 3372, 1632	247 (4.65), 295 sh (3.93), 368 sh (3.53)	2.09 (s, 3H, CH ₃), 4.53 (s, 2H, NH ₂), 6.66 (s, 1H, 5-H), 6.90-7.62 (m, 18H, ArH)
3i	3472, 3372, 1634	250 (4.66), 314 sh (3.92), 368 sh (3.67)	3.57 (s, 3H, OCH ₃), 4.56 (s, 2H, NH ₂), 6.66 (s, 1H, 5-H), 6.66-7.61 (m, 18H, ArH)
3j	3468, 3372, 1636	247 (4.70), 298 sh (3.98), 377 (3.61)	4.70 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 7.05-7.64 (m, 18H, ArH)
3k	3468, 3372, 1636	248 (4.70), 298 sh (3.98), 373 (3.64)	4.65 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 7.11-7.63 (m, 18H, ArH)
3l	3496, 3392, 1640	247 (4.63), 294 sh (4.07), 370 sh (3.52)	2.21 (s, 3H, CH ₃), 2.26 (s, 3H, CH ₃), 4.53 (s, 2H, NH ₂), 6.72 (s, 1H, 5-H), 6.97-7.71 (m, 17H, ArH)
3m [b]	3488, 3392, 1646	244 (4.64), 292 sh (4.01), 373 (3.57)	4.90 (s, 2H, NH ₂), 6.69 (s, 1H, 5-H), 7.03-7.87 (m, 18H, ArH)
3n	3488, 3392, 1648	247 (4.67), 373 sh (3.59)	2.09 (s, 3H, CH ₃), 4.85 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 6.90-7.86 (m, 17H, ArH)
3o	3492, 3384, 1636	251 (4.64), 314 sh (3.89), 368 sh (3.66)	3.57 (s, 3H, OCH ₃), 4.86 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 6.66-7.86 (m, 17H, ArH)
3p	3484, 3384, 1646	247 (4.68), 296 sh (4.00), 376 (3.60)	4.97 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 7.03-7.87 (m, 17H, ArH)
3q	3516, 3408, 1640	248 (4.70), 370 (3.62)	4.94 (s, 2H, NH ₂), 6.66 (s, 1H, 5-H), 7.02-7.86 (m, 17H, ArH)
3r	3504, 3412, 1652	246 (4.62), 370 (3.56)	2.13 (s, 3H, CH ₃), 2.19 (s, 3H, CH ₃), 4.76 (s, 2H, NH ₂), 6.66 (s, 1H, 5-H), 6.92-7.88 (m, 16H, ArH)
3s	3504, 3412, 1656	248 (4.68), 377 (3.63)	5.02 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 7.06-7.90 (m, 16H, ArH)
3t	3492, 3392, 1652	248 (4.67), 379 (3.60)	5.02 (s, 2H, NH ₂), 6.67 (s, 1H, 5-H), 6.99-7.90 (m, 16H, ArH)

[a] 5-H Denotes the proton in position 5. [b] Mass spectra: (70 eV), m/z (%) **3a** 493 (100) [M⁺], 105 (81) [PhCO⁺], 77 (41) [Ph⁺], **3g** 493 (100) [M⁺], 105 (20) [PhCO⁺], 77 (21) [Ph⁺], **3m** 561 (100) [M⁺], 105 (75) [PhCO⁺], 77 (47) [Ph⁺].

4.27-5.02 ppm and the singlet of the proton in position 5 at 6.64-6.72 ppm which is shifted upfield in comparison to the signals of the protons bonded to the aryl substituents by the known *para*-shielding effect of the amino group [7]. Finally, the extended aromatic π -system is responsible for a strong uv absorption at 242-251 nm with shoulders up to 379 nm.

The mechanism of the ring transformations observed can be explained in analogy to the reaction of the pyrylium salts **1** with 4-nitrobenzyl cyanide [4] and pyridyl acetonitriles [5]. Under the action of methanolate the trifluoromethylbenzyl cyanides **2** are deprotonated to the appropriate carbanions which as carbon nucleophiles are added to the preferred position 2 [3] of the 2,4,6-triarylpyrylium cations **1** to give the 2H-pyran intermediates **4**. These pyrans are usually unstable [8] and an electrocyclic ring

opening to the acyclic valence isomers **5** occurs. By deprotonation, ring closure and [1.3] proton shift then the 2-aminobenzophenones **3** are formed *via* the anions **6** and cyclohexadienes **7**. For a successful ring transformation the trifluoromethylbenzyl cyanides used must have a sufficient acidity which possess the cyanides **2** but not the 3-(trifluoromethyl)benzyl cyanide so that with the latter one no ring transformation occurs. In the course of the ring transformation **1** + **2** \rightarrow **3** a benzene ring is built up from four carbon atoms of the pyrylium cation and two C-atoms of the trifluoromethylbenzyl cyanide by connection of the former positions 2 and 4 of the heterocycle by a C₂-chain. According to the nomenclature proposed for the classification of pyrylium ring transformations [3a] the reaction can be characterized as a 2,5-[C₄+C₂] transformation.



EXPERIMENTAL

The melting points were measured on a Böttius hot stage apparatus and are corrected. The 1H nmr spectra were recorded on a Bruker AM 250 spectrometer (250 MHz, DMSO- d_6 , 25°, HMDSO as internal standard), ir spectra were obtained on a Zeiss M 80 spectrophotometer (in potassium bromide) and uv spectra on a Zeiss M 40 instrument (acetonitrile, 25°). Mass spectra were determined on a Finnigan MAT 111A spectrometer (70 eV, electron impact). The pyrylium salts **1a** [9], **1b** [10], **1c** [11], **1d** [12], **1e** [13] and **1f-h** [14] were prepared according to literature procedures. 2-(Trifluoromethyl)benzyl cyanide (**2a**), 4-(trifluoromethyl)benzyl cyanide (**2b**) and 3,5-bis(trifluoromethyl)benzyl cyanide (**2c**) were provided by Fluka.

Preparation of Trifluoromethyl Substituted 2-Amino-3,4,6-triarylbenzophenones **3** from 2,4,6-Triarylpyrylium Salts **1** and Trifluoromethylbenzyl Cyanides **2**. General Procedure.

To a sodium methanolate solution, prepared by dissolving sodium metal (0.23 g, 10 mmoles) in absolute methanol (40 ml), 2.5 mmoles pyrylium perchlorate **1** and 7.5 mmoles trifluoromethylbenzyl cyanide **2** were added. The reaction mixture was then heated under reflux for 1 hour. The 2-aminobenzophenones

3 formed crystallized in some cases from the hot reaction mixture; otherwise their crystallization was initiated by cooling. They were filtered off by suction, washed with methanol and dissolved in a minimal amount of hot chloroform, from which analytical pure compounds **3** were precipitated by addition of *n*-hexane.

Acknowledgement.

The financial support by the Fonds der Chemischen Industrie is gratefully appreciated.

REFERENCES AND NOTES

- [1] Part VIII: T. Zimmermann, *Synthesis*, 252 (1994).
- [2] D. A. Walsh, *Synthesis*, 677 (1980).
- [3a] A. T. Balaban, A. Dinculescu, G. N. Dorofeenko, G. W. Fischer, A. V. Koblik, V. V. Mezheritskii and W. Schroth, Pyrylium Salts. Syntheses, Reactions and Physical Properties, *Advances in Heterocyclic Chemistry*, Suppl. 2, Academic Press, New York, 1992; [b] W. Schroth, W. Dölling and A. T. Balaban, in Houben-Weyl, Vol E7b/2, R. P. Kreher, ed, Thieme, Stuttgart, 1992, pp 755-1014.
- [4] T. Zimmermann and P. G. Jones, *J. Prakt. Chem./Chem.-Ztg.*, 335, 351 (1993).
- [5] T. Zimmermann, *J. Prakt. Chem./Chem.-Ztg.*, 335, 644 (1993).
- [6] For reviews see: M. R. C. Gerstenberger and A. Haas, *Angew. Chem.*, 93, 659 (1981), *Angew. Chem., Int. Ed. Engl.*, 20, 647, (1981); J. T. Welch, *Tetrahedron*, 43, 3123 (1987); J. P. Begue and D. Bonnet-Delpon, *Tetrahedron*, 47, 3207 (1991) and references cited therein.
- [7] J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Vol 2, Pergamon Press, Oxford, 1966, p 750.
- [8] J. Kuthan, *Adv. Heterocyclic Chem.*, 34, 145 (1983).
- [9] A. T. Balaban and C. Toma, *Tetrahedron*, Suppl. 7, 1 (1966).
- [10] A. Mistr, M. Vavra, J. Skoupy and R. Zahradnik, *Collect. Czech. Chem. Commun.*, 37, 1520 (1972).
- [11] R. Wizinger, S. Losinger and P. Ulrich, *Helv. Chim. Acta*, 39, 5 (1956).
- [12] K. Dimroth, C. Reichardt, T. Siepmann and F. Bohlmann, *Liebigs Ann. Chem.*, 661, 1 (1963).
- [13] G. N. Dorofeenko, S. V. Krivun and V. V. Mezheritskii, *Zh. Obshch. Khim.*, 35, 632 (1965).
- [14] G. W. Fischer and M. Herrmann, *J. Prakt. Chem.* 326, 287 (1984).