Pergamon

Tetrahedron Letters 43 (2002) 8051–8054

TETRAHEDRON
LETTERS

Convenient access to 1,3,5-triaroylbenzenes

Delphine Joseph,[a,*] Raphael Jankowski,[a] Damien Prim,[b] Jacqueline Mahuteau[a] and Angèle Chiaroni[c]

[a] *BioCIS ESA 8076, Centre d'Etudes Pharmaceutiques, Université Paris-Sud, 5, rue Jean-Baptiste Clément, F-92296 Châtenay-Malabry Cedex, France*
[b] *Laboratoire SIRCOB, UPRES A CNRS 8086, Bâtiment Lavoisier, Université de Versailles, 45, avenue des Etats-Unis, F-78035 Versailles Cedex, France*
[c] *Institut de Chimie des Substances Naturelles, CNRS, avenue de la Terrasse, F-91198 Gif-sur-Yvette Cedex, France*

Received 29 July 2002; revised 12 September 2002; accepted 13 September 2002

Abstract—The unusual transformation of β-aryl-β-haloacroleins into valuable triaroylbenzenes is reported by the first time. The convenient sequence takes advantage on the one step access to triaroylbenzenes. This work establishes that the presence of amine is required for the trimerization procedure since it is involved in the formation of iminium–enamine intermediate A. © 2002 Elsevier Science Ltd. All rights reserved.

The triacylbenzene entity is an aromatic common core to molecules that exhibit various properties. For example, 1,3,5-triacylbenzenes have been isolated from *Cochlospermum tinctorium rhizome* known in African traditional medicine for the treatment of liver diseases.[1] Such compounds were found to form crystalline inclusion complexes[2] and to induce non linear optical as well as redox properties.[3] They are also key intermediates in the preparation of super-high-spin organic molecules with ferro- and opto-magnetic properties.[4] Not surprisingly several efforts has been devoted to the development of synthetic methodology directed toward the efficient preparation of triaroylbenzenes. In this regard, two general strategies have been utilized that rely on either functionalization of preexisting central benzene ring[5] or cyclotrimerization of β-aminoketones or benzoylacetylenes.[2c,4d,6] During the course of studies devoted to the reactivity of chloroacroleins,[7] we discovered that β-aryl-β-haloacroleins successfully cyclotrimerized, upon heating to afford the 1,3,5-triaroylbenzene core. The strategy reported herein allows a convenient and rapid access to triaroylbenzenes substituted by valuable functional groups, that complement the existing methods. Attempts to clarify the mechanism evidenced the formation of an iminium–enamine intermediate in the early stage of the reaction. The X-ray crystal structure of triaroylbenzene **11a** (Fig. 1) reveals an uncommon inclusion like dimer where two molecules arranged by means of strong hydrogen bonds involving chlorine atoms rather than the more classical oxygen atom.[2]

β-Aryl-β-haloacroleins **1**–**10** are well known, easy accessible, reactive compounds.[8] Their reactivity towards nucleophiles (N, O, S, Se) has been mostly studied providing an access to numerous heterocycles through 1,4-addition–elimination mechanisms.[7a–c,9] Surprisingly, refluxing β-(4-chlorophenyl)-β-chloroacrolein **1** in DMF led to a complete disappearance of the starting material in 1 h and to the formation of unexpected triaroylbenzene **11a** in 61% yield (Scheme 1). Several β-aryl-β-haloacrolein derivatives **1**–**10** have been subjected to identical reaction conditions giving rise to new 1,3,5-triaroylbenzenes substituted by valuable functional groups (Table 1).[10] The use of the above-mentioned conditions allowed the reaction of either β-chloro- or β-bromoacrolein leading to the formation of the desired compound **11a** in similar yields and reaction time (entries 1 and 2).

We next examined the influence of substituent R^1 of the starting acrolein. Triaroylbenzenes substituted by halides (**11a**, **e** and **f** in entries 1, 6 and 7) and nitro groups (**11c**, entry 4) as well as the non substituted structure (**11b**, entry 3) could be obtained in 31–71% yield. Only the well known highly unstable methoxy-subtituted acrolein did not afford the expected triaroylbenzene **11d** (entry 5). Whether other substituents R^2 such as carboxylic esters were also able to furnish trimerization products was next examined.

---

* Corresponding author. Tel.: 33(0)1 46835730; fax: 33(0)1 46835652; e-mail: delphine.joseph@cep.u-psud.fr

PII: S0040-4039(02)01967-6

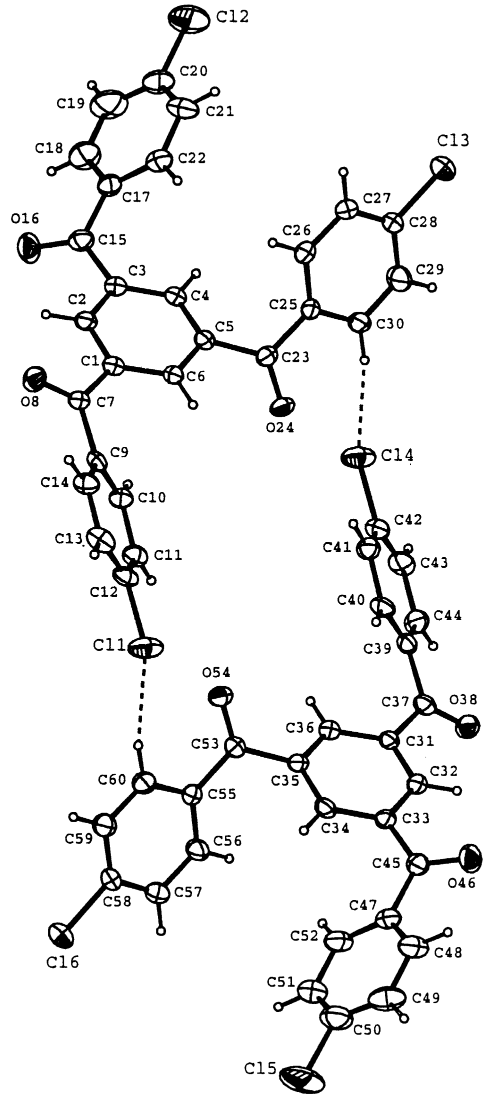
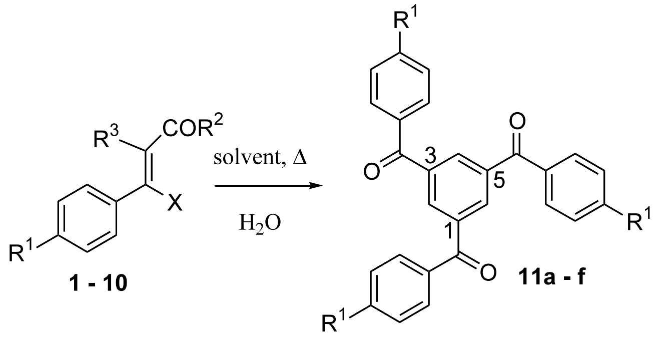


Figure 1. ORTEP drawing of the X-ray crystal structure of **11a** showing dimerization via two CH···Cl hydrogen bonds in the solid state. Displacement ellipsoids are shown at the 30% level. Estimation of the dimer cavity dimensions: O24···Cl4 = 3.810(5), O54···Cl1 = 3.768(5), O24···O54 = 6.770(8), C7···Cl4 = 8.535(6), C37···Cl1 = 8.525(7), Cl1···Cl4 = 9.461(4), C7···C37 = 11.291(9) and C30···C60 = 11.909(13) Å.



Scheme 1.

Requisite carboxylic ester **8** was prepared from acrolein **1** as reported[7d] and subjected to identical reaction conditions. No traces of triaroylbenzene could be detected and starting compound was recovered unchanged. This experiment revealed that the carboxaldehyde moiety was strictly required for this transformation (Table 1, entry 8). It was also established that the presence of an additional substituent on the acrolein moiety precludes the formation of triaroylbenzenes (entry 9 and 10). Surprisingly, in DMSO at 150°C or in refluxing THF for 1 h, acrolein **2** did not afford compound **11a**. Since dimethylamine may be produced by heating DMF and dialkylamines have been shown to catalyze cyclotrimerization of ethynylketones,[6a] the aforementioned reactions, were run in the presence of 1 and 2 equiv. of diethylamine. In fact, triaroylbenzene **11a** was produced in 63% yield when acrolein **2** was heated at 150°C in DMSO in presence of 2 equiv. of diethylamine. The same reaction conducted in refluxing THF in presence of 2 equiv. of diethylamine was also successful, indicating that high temperatures are not required. If decreasing the initial amount of diethylamine to 1 equiv. lead to a small decrease of the reaction rate, attempts to use catalytic amount of diethylamine failed. Consequently the presence of diethylamine is strictly required in the trimerization of β-aryl-β-haloacroleins. In the light of these results, one can expect the formation of intermediate such as **A** by two iterative nucleophilic attack at both β-haloacroleins reactive sites, in an early stage of the reaction (Scheme 2).[11] Despite our efforts, we were not able to isolate intermediate **A** from reaction mixtures. The structure of **A** was however undoubtedly confirmed by NMR analysis. The characteristic deshielding/shielding alternate along the diene chain (169.3–92.3–159.4 ppm) is consistent with the formation of both iminium and enamine moieties.[12] An 11 Hz coupling constant confirmed a *Z* configuration of the enamine double bond. Moreover NOE experiments evidenced the diene conformation shown in Scheme 2.

To show that **A** was one of the intermediates of the tranformation, it was dissolved in deuterated DMSO and heated at 60 and 130°C. The reaction was then monitored by ^{1}H NMR. Surprisingly, **A** was recovered unchanged, showing high degree of stability even under hard conditions and prolonged heating time. Therefore, a rapid decrease of intermediate **A** with concomitant formation of triaroylbenzene **11a** was obtained after stepwise addition of 1 and 2 equiv. of starting acrolein **1** (Scheme 2). Thus, these findings showed that **A** is one of the intermediates formed during the reaction. However, at this stage, the way to produce the triaroylbenzene core from **A** in the reaction conditions is still unclear.[13]

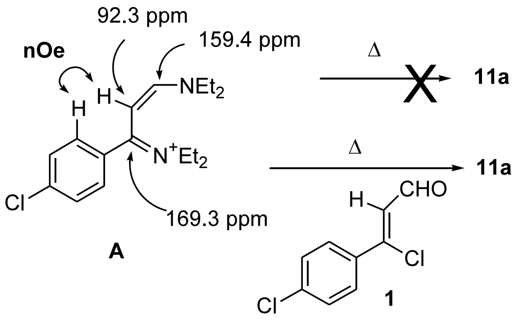
The crystal structure of compoud **11a** is shown in Fig. 1.[14] It is worth noting that the two molecules of the unit-cell labelled (C1–C30) and (C31–C60) are assembled in a nearly centrosymmetric dimer, by means of two strong hydrogen bonds involving the chlorine atoms Cl1 and Cl4 with the nearest C-H groups, C60-H and C30-H, respectively (distances Cl1···C60 = 3.750(8) Å, Cl1···H60 = 2.88 Å, angle Cl1···H–C60 = 157.1°;

Table 1. Cyclotrimerization of acroleins **1**–**11**

Entry	R^1	R^2	X	R^3	Acrolein	Time (h)	Compound	Yield (%)
1	Cl	H	Cl	H	**1**	1	**11a**	61
2	Cl	H	Br	H	**2**	0.5	**11a**	59
3	H	H	Cl	H	**3**	1	**11b**	31
4	NO_2	H	Cl	H	**4**	2	**11c**	45
5	MeO	H	Cl	H	**5**	0.5	**11d**	–[a]
6	Br	H	Cl	H	**6**	3	**11e**	65
7	F	H	Cl	H	**7**	4	**11f**	71
8	Cl	OEt	Cl	H	**8**	24	**11g**	–[b]
9	H	H	Cl	Me	**9**	24	**11h**	–[b]
10	H	H	Cl	Ph	**10**	24	**11i**	–[b]

[a] Severe resinification occurred.

[b] Starting material recovered unchanged.



Scheme 2.

Cl4···C30=3.736(9) Å, Cl4···H30=2.84 Å, angle Cl4···H-C30=160.5°). The mean values of the interplanar distances between the phenyl rings (C1–C6) and (C31–C36), (C9–C14) and (C39–C44), (C25–C30) and (C55–C60) are 11.224, 8.546 and 13.943 Å, respectively. In contrast to inclusion complexes recently described by Pigge[2], the distances O24···C41 of 4.057(8) Å and O54···C11 of 4.046(9) Å are too long to allow classical hydrogen bonding. The dihedral angles between the central benzene ring (C1–C6) and the three other phenyl rings are 54.0° for ring (C9–C14), 48.5° for ring (C17–C22) and 123.0° for ring (C25–C30), respectively. Similar values are found in the second monomer: 54.2, 45.6 and 122.5°, respectively.

In conclusion, we have shown that a fast and convenient preparation of valuable 1,3,5-triaroylbenzenes is now available starting from β-aryl-β-haloacroleins. The crucial role played by the amine in the trimerization procedure has been outlined and an enamine–iminium salt intermediate has been characterized. The X-ray crystal structure of triaroylbenzene **11a** showed an unusual dimeric arrangement of the triaroylbenzene units.

Acknowledgements

The authors thank the CNRS for financial support.

References

1. Diallo, B.; Vanhaelen-Fastré, R.; Vanhaelen, M. *Phytochemistry* **1991**, *30*, 4153.
2. (a) Pigge, F. C.; Zheng, Z. *Tetrahedron Lett.* **2001**, *42*, 8259; (b) Pigge, F. C.; Ghasedi, F.; Zheng, Z.; Rath, N. P.; Nichols, G.; Chickos, J. S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2458; (c) Pigge, F. C.; Zheng, Z.; Rath, N. P. *N. J. Chem.* **2000**, *24*, 183; (d) Pigge, F. C.; Ghasedi, F. *Tetrahedron Lett.* **2000**, *41*, 6545; (e) Pigge, F. C.; Ghasedi, F.; Rath, N. P. *Tetrahedron Lett.* **1999**, *40*, 8045.
3. Lambert, C.; Nöll, G.; Schmälzlin, E.; Meenholz, K.; Braüchle, C. *Chem. Eur. J.* **1998**, *4*, 2129.
4. See for example: (a) Kwak, S. Y.; Ahn, D. U. *Macromolecules* **2000**, *33*, 7557; (b) Wienk, M. M.; Janssen, R. A. J. *J. Am. Chem. Soc.* **1997**, *119*, 5398; (c) Matsuda, K.; Nakamura, N.; Inoue, K.; Koga, N.; Iwamura, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1483; (d) Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *Chem. Eur. J.* **1996**, *2*, 259; (e) Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550; (f) Matsuda, K.; Inoue, K.; Koga, N.; Nakamura, N.; Iwamura, H. *Mol. Cryst. Liq. Cryst.* **1994**, *253*, 33.
5. Jütz, C.; Wagner, R.-M.; Kraatz, A.; Göbering, H.-G. *Liebigs Ann. Chem.* **1975**, 874.
6. (a) Matsuda, K.; Nakamura, N.; Iwamura, H. *Chem. Lett.* **1994**, 1765; (b) Murahashi, S.-I.; Mitsue, Y.; Tsumiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3285; (c) Balasubramanian, K. K.; Selvaraj, P. S.; Venkataramani, P. S. *Synthesis* **1980**, 29; (d) Harmish, H. *Liebigs Ann. Chem.* **1972**, *765*, 8; (e) Croxall, W. J.; Van Hook, J. O. *J. Am. Chem. Soc.* **1949**, *71*, 2422.
7. (a) Kirsch, G.; Prim, D.; Leising, F.; Mignani, G. *J. Heterocyclic Chem.* **1994**, *31*, 1005; (b) Prim, D.; Joseph, D.; Kirsch, G. *Liebigs Ann.* **1996**, 239; (c) Prim, D.; Joseph, D.; Kirsch, G. *Phosphorus, Sulfur, Silicon* **1994**, *91*, 137; (d) Prim, D.; Fuss, A.; Kirsch, G.; Silva, A. M. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1175.
8. β-Aryl-β-haloacroleins can be readily prepared in one step by addition of Vilsmeier–Haack reagent to commercially available α-methylene ketones (see Ref. 7a) or acetylenic compounds, see: Ziegenbein, W.; Franke, W. *Angew. Chem.* **1959**, *71*, 573.
9. Marson, C. M.; Giles, P. R. *Synthesis using Vilsmeier Reagents*; CRC Press, 1994 and references cited therein.

10. All new compounds showed satisfactory spectroscopic and analytical data. Typical procedure for triaroylbenzene **11a**: β-aryl-β-haloacroleins (1 mmol), diethylamine (2 mmol) were refluxed in degassed THF for the time indicated in Table 1. The reaction mixture was poured into ice cold water and the precipitate collected by filtration. Compound **11a** was purified by flash column chromatography using petroleum ether/diethylether 7:3 as eluent. **11a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.51 (d, 3×2H), 7.77 (d, 3×2H), 8.34 (s, 3×1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.1, 131.4, 133.8, 134.5, 138.1, 140.1, 193.4. IR (CH_2Cl_2) ν (CO): 1664 cm^{-1}. UV (CH_2Cl_2) λ_{max}: 267 nm. Mass: $m/z = 492.1$. Anal. calcd for $C_{27}H_{15}Cl_3O_3$: C, 65.68; H, 3.06. Found: C, 65.59; H, 3.01%.
11. Nucleophilic attack from amines on β-haloacroleins can occur at C-4 and/ or at the carboxaldehyde group leading to enamines and/or imines or iminium salts, respectively. Weissenfels, M. *Z. Chem.* **1964**, *4*, 458. Terent'ev, A. P.; Volotina, M. A.; Kudryashova, V. A. *Dokl. Akad. Nauk SSR* **1965**, *164*, 115. *Chem. Abs.* **1965**, *63*, 16290c.
12. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; 3rd ed.; VCH: Weinheim, 1987; p. 238.
13. The presence of other possible intermediates such as α-formylacetophenones, also known to trimerize[6d] and which could arose from addition of released water on **1** or **A** could not be evidenced.
14. *Crystallographic data*. Small colorless crystal (0.26×33× 0.36 mm). $C_{27}H_{15}Cl_3O_3$, $M_w = 493.74$. Orthorhombic system, racemic space group $Pca2_1$, $Z = 8$: so, there are two molecules in the asymmetric unit. Cell parameters: $a = 10.396(7)$, $b = 9.300(8)$, $c = 48.014(34)$ Å, $V = 4642$ Å^3; $D_{calcd} = 1.413$ g cm^{-3}, $F(000) = 2016$, λ (CuKα) = 1.5418 Å, $\mu = 3.80$ mm^{-1}, no decay, absorption ignored. Intensity data were collected with a Nonius CAD4 diffractometer up to $\theta = 67°$ (h: 0–12, $-10 \leq k \leq 11$, l: 0–57). From the 7657 reflections measured, 4201 were independent ($R_{int} = 0.047$) of which 2677 were considered as observed having $I \geq 2\sigma(I)$. The structure was solved by direct methods using program *SHELXS86*[15] and refined by full-matrix least-squares based upon unique F^2 with program *SHELXL93.*[16] Hydrogen atoms were fitted at theoretical positions and assigned an isotropic displacement parameter equivalent to 1.20 that of the bonded atom. Refinement converged to $R_1(F) = 0.0482$ for the 2677 observed reflections and $wR_2(F^2) = 0.1267$ for all the 4201 data with goodness-of-fit $S = 1.035$. Residual electron density was found between −0.25 and 0.24 e Å^{-3}. In the crystal, the molecules are closely packed, no channel was observed. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 190303.
15. Sheldrick, G. M. *SHELXS86. Acta Crystallogr. A* **1990**, *46*, 467–473.
16. Sheldrick, G. M. *SHELXL93. Program for the Refinement of Crystal Structures*; University of Göttingen, Germany, 1993.