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Graphical Abstract

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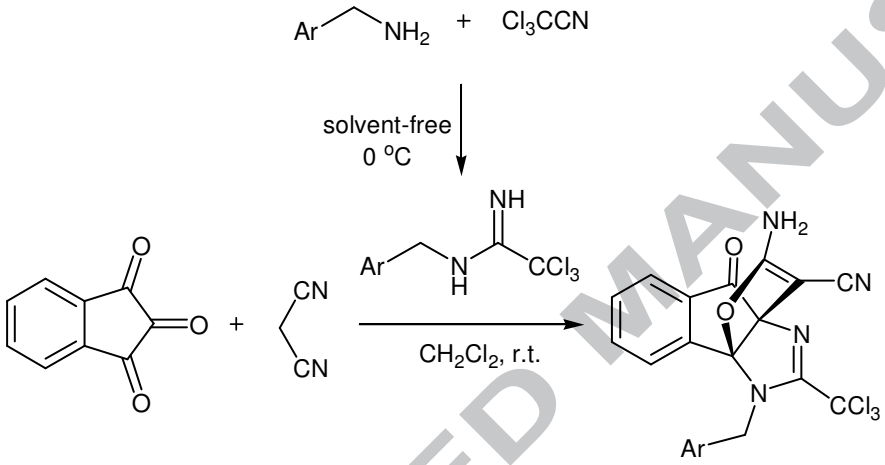

Tandem synthesis of trichloromethylated [3.3.3]propellanes from trichloroacetamidines and a ninhydrin-malononitrile adduct

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ABSTRACT

The trichloroacetamidine intermediates, generated by addition of benzylamine derivatives to trichloroacetonitrile, react with the Knoevenagel condensation product of ninhydrin and malononitrile to afford trichloromethylated [3.3.3]propellanes, in good yields. When benzylamine was used, a plane-symmetrical spiro-compound was obtained.

Keywords:

[3.3.3]propellanes

trichloroacetonitrile

ninhydrin

malononitrile

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Propellanes are defined as compounds having three non-zero bridges and one zero bridge between a pair of bridgehead carbons. The interesting chemical and physical properties of propellanes stem from their fascinating topology.[1] The propellane skeleton is present in some natural products, and bioactive aza-propellane skeletons have been reported. Various methods for the synthesis of propellanes have been described.[2]

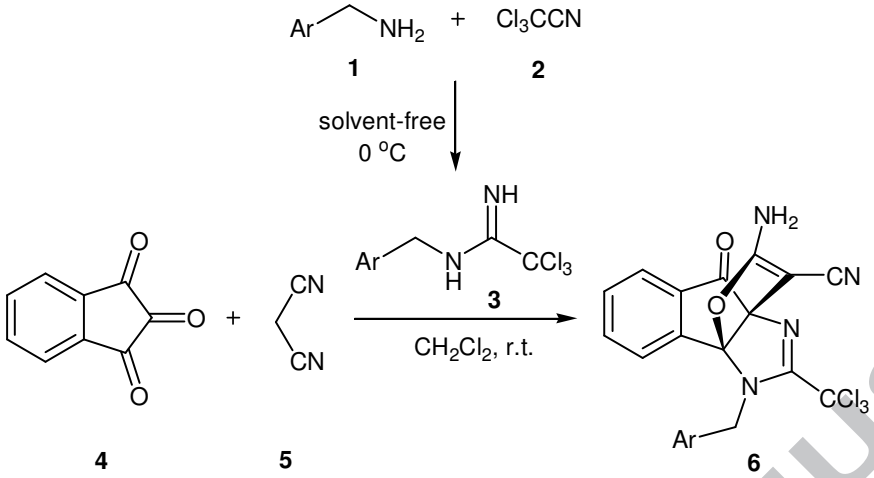
The presence of a trihalomethyl group in a molecule can result in significant changes in its physical, chemical, and biological properties. Many bioactive trihalomethylated compounds have found important applications in medicine and agriculture.[3]

As part of our studies on the development of new routes for the synthesis of trihalomethylated compounds,[4] we herein report a tandem method for the synthesis of trichloromethylated [3.3.3]propellanes from trichloroacetamidine derivatives and the Knoevenagel condensation product of ninhydrin and malononitrile.

Reaction of benzylamine derivatives **1** with trichloroacetonitrile (**2**), under solvent-free conditions, produced trichloroacetamidine derivatives **3** (Table 1). Addition of amidines **3** to a mixture of ninhydrin (**4**) and malononitrile (**5**) in CH_2Cl_2 at room temperature led to the formation of [3.3.3]propellanes **6**.[5]

Table 1

Synthesis of trichloromethylated [3.3.3]propellanes **6**



Entry	**1, 3, 6**	Ar	Yield of **6** (%)
1	**a**	4-Me-C_6H_4	85
2	**b**	4-MeO-C_6H_4	91
3	**c**	4-Br-C_6H_4	81
4	**d**	4-Cl-C_6H_4	88
5	**e**	2-Cl-C_6H_4	78

The structures of products **6** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectral data and by single-crystal X-ray analysis of **6a**. The ^{1}H NMR spectrum of **6a** showed two sharp singlets (δ 2.34 and δ 7.10) for the methyl and amino protons, and an AB-quartet for the methylene (δ 5.12) protons. In the ^{13}C NMR spectrum, signals corresponding to the trichloromethyl, cyanide, and carbonyl groups of **6a** were observed at δ 89.4, 116.1 and 193.9, respectively.[6]

Unequivocal evidence for the structure of **6a** was obtained from single-crystal X-ray analysis.[7] The ORTEP[8] diagram of **6a** is shown in Figure 1. The structure was deduced from the crystallographic data and those of **6b-e** were assumed to be analogous on account of their NMR spectroscopic similarities.

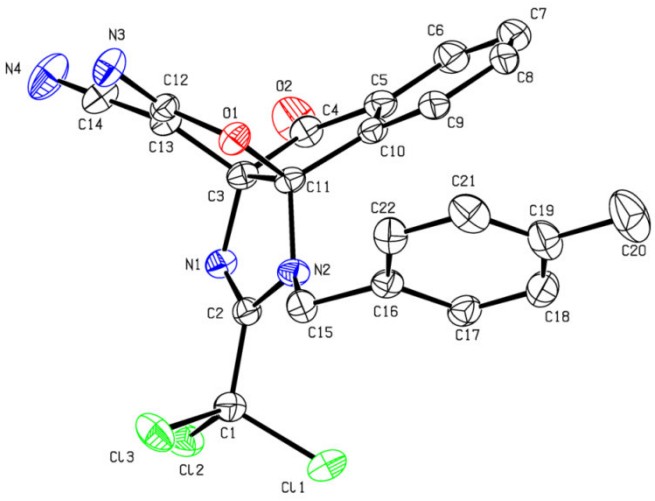
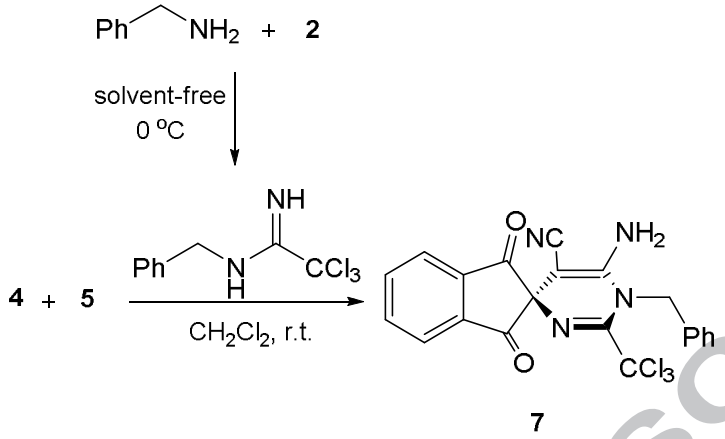


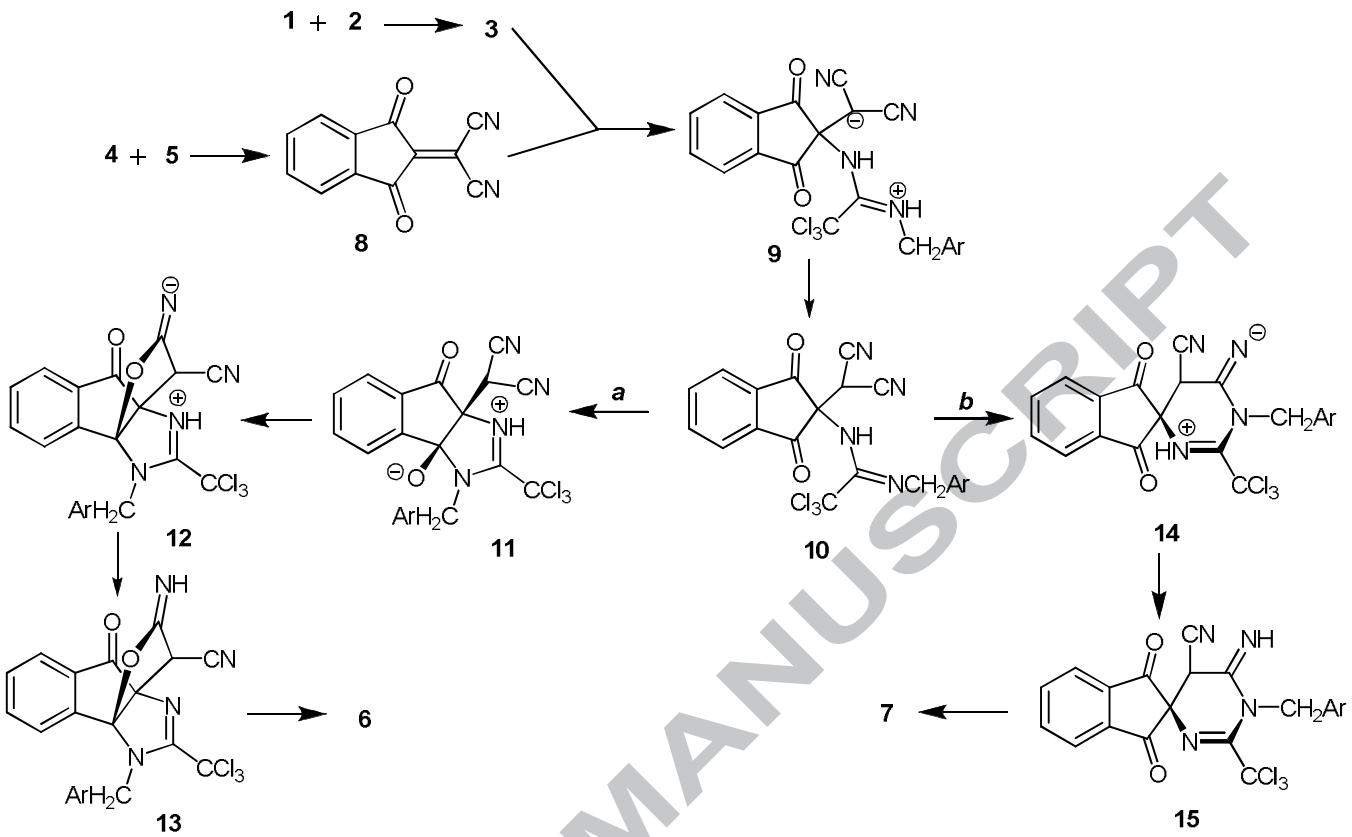
Figure 1. X-ray crystal structure (ORTEP) of **6a**.

When benzylamine was used, plane-symmetrical 6'-amino-1'-benzyl-1,3-dioxo-2'-(trichloromethyl)-1,3-dihydro-1'*H*-spiro[indene-2,4'-pyrimidine]-5'-carbonitrile (**7**), instead of the [3.3.3]propellane system, was obtained in 75% yield (Scheme 1).[6] The ^{13}C NMR spectrum of **7** was consistent with the presence of a local plane of symmetry in the ninhydrin residue of the molecule. In addition, the observation of a singlet for the benzylic protons in the ^{1}H NMR spectrum of **7** is in accord with this conclusion.



Scheme 1. Synthesis of spiro-compound **7**.

Although the detailed mechanism of this reaction remains to be clarified, a plausible mechanism for the formation of products **6** and **7** is shown in Scheme 2. It is conceivable that the reaction involves the initial formation of Knoevenagel adduct **8** between ninhydrin and malononitrile, which reacts with acetamidine **3** to produce **9**. This intermediate undergoes proton-transfer to afford **10**. Intermediate **10** can follow two paths: a) attack of the nitrogen atom on the carbonyl group, followed by formation of the propellane system **12**, which is converted into product **6** by imine-enamine tautomerization in **13**; and b) attack of the nitrogen atom on one of the cyanide groups to generate spiro-system **14**, which affords product **7** *via* a proton shift and imine-enamine tautomerization (Scheme 2).



Scheme 2. Proposed mechanisms for the formation of products **6** and **7**.

It is not clear at present why benzylamine gives the spiro-compound **7** and 4-methylbenzylamine gives the [3.3.3]propellane **6a**. Since there is very little difference between benzylamine and 4-methylbenzylamine, we are unable to explain this difference in terms of steric and electronic effects. However, the carbon atom of the carbonyl group in intermediate **10** is a "harder" electrophile compared to the cyano group. Thus, benzylamine, being a "softer" nucleophile, prefers to attack the cyano carbon atom of **10** (see Scheme 2).

In conclusion, the tandem reaction of trichloroacetonitrile, substituted benzylamines, ninhydrin and malononitrile leads to functionalized trichloromethylated [3.3.3]propellanes.

When benzylamine was used, a plane-symmetrical spiro-compound was obtained. The procedure described here has the advantage that the reaction is performed under neutral conditions.

References and notes

1. a) Ginsburg, D. *Propellanes: Structure and Reactions*; Verlag Chemie: Weinheim, 1975. b) Navarro, R.; Reisman, S. E. *Org. Lett.* **2012**, *14*, 4354. c) Dyker, G.; Körning, J.; Bubenitschek, P.; Jones, P. G. *J. Chem. Res.* **1997**, 132. d) Wiberg, K. B. *Chem. Rev.* **1989**, *89*, 975.
2. a) Miao, M.; Cao, J.; Zhang, J.; Huang, X.; Wu, L. *J. Org. Chem.* **2013**, *78*, 2687. b) Zhang, L. J.; Yan, C. G. *Tetrahedron* **2013**, *69*, 4915. c) Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 17877. d) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *J. Org. Chem*. **2012**, *77*, 4385. e) Rezvanian, A.; Alizadeh, A. Zhu, L. G. *Synlett* **2012**, 2526. f) Asahi, K.; Nishino, H. *Tetrahedron* **2008**, *64*, 1620. g) Almog, J.; Stepanov, N.; Dubnikova, F. *Tetrahedron Lett.* **2008**, *49*, 1870. h) Nowicka-Scheibe, J.; Sośnicki, J. G.; Sawka-Dobrowolska, W. *Tetrahedron Lett.* **2007**, *48*, 5439. i) Asahi, K.; Nishino, H. *Tetrahedron Lett.* **2006**, *47*, 7259. j) Lee, H. Y.; Moon, D. K.; Bahn, J. S. *Tetrahedron Lett.* **2005**, *46*, 1455.
3. a) Flores, A. F. C.; Brondani, S.; Zanatta, N.; Rosa, A.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 8701. 22. b) Martins, M. A. P.; Beck, P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Blanco, R. F.; Peres, R.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2002**, *43*, 7005. c) Chambers, R. D.; Sargent, C. R. *Adv. Heterocycl. Chem.* **1991**, *28*, 1. d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
4. a) Yavari, I.; Nasiri-Gheidari, S. *Helv. Chim. Acta* **2011**, *94*, 811. b) Yavari, I.; Sabbaghan, M.; Hossaini, Z.; Ghazanfarpour-Darjani, M. *Helv. Chim. Acta* **2008**, *91*, 1144. c) Yavari, I.;

Sabbaghan, M.; Hossaini, Z. *Monatsh. Chem.* **2008**, *139*, 625. d) Yavari, I.; Djahaniani, H.; Nasiri, F. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1499.

5. General procedure for the preparation of compounds **6** and **7**: benzylamine derivative **1** (2 mmol) was added to Cl_3CN (**2**) (2 mmol) at 0 ºC and the mixture stirred for 5 min. The resulting precipitate was added to a stirred solution of ninhydrin (**4**) (2 mmol) of and malononitrile (**5**) (2 mmol) in CH_2Cl_2 (15 mL) at room temperature. After completion of the reaction [about 4 h, TLC (EtOAc/hexane, 1:5) monitoring], the formed solid was filtered and the residue rinsed with CH_2Cl_2 to afford the pure product.

6. **2-Amino-9-(4-methylbenzyl)-4-oxo-10-(trichloromethyl)-4*H*-3a,8b-(azenomethenoimino)indeno[1,2-*b*]furan-3-carbonitrile (6a):** Pale yellow powder, mp (dec.): 160 ºC. Yield 0.40 g, 85%. IR (KBr): 2196, 1729, 1657, 786, 661. ^{1}H NMR (300 MHz, acetone-d_6): δ 2.34 (3H, s, Me), 5.12 (2H, ABq, J = 17.3 Hz, $\Delta\nu_{AB}$ = 105.3 Hz, CH_2), 7.10 (2H, s, NH_2), 7.17 (2H, d, J = 7.9 Hz, CH), 7.31 (2H, d, J = 7.9 Hz, CH), 7.34 (1H, d, J = 2.0 Hz, CH), 7.74 (2H, m, CH), 7.94 (1H, m, CH). ^{13}C NMR (75 MHz, acetone-d_6): δ 21.1 (Me), 49.4 (CH_2), 56.2 (C), 88.9 (C), 89.4 (CCl_3), 111.5 (C), 116.1 (CN), 126.1 (CH), 126.9 (CH), 128.3 (CH), 130.0 (CH), 132.5 (CH), 133.8 (C), 136.8 (CH), 137.5 (C), 138.0 (C), 144.0 (C), 160.3 (C), 168.2 (C), 193.9 (C=O). MS (EI, 70 eV): *m/z* (%) = 301 (27), 285 (32), 260 (35), 219 (23), 185 (11), 155 (24), 117 (10), 105 (100), 91 (44), 83 (10), 77 (55). Anal. Calcd for $C_{22}H_{15}Cl_3N_4O_2$ (473.74): C, 55.78; H, 3.19; N, 11.83. Found: C, 56.11; H, 3.22; N, 11.91.

6'-Amino-1'-benzyl-1,3-dioxo-2'-(trichloromethyl)-1,3-dihydro-1'*H*-spiro[indene-2,4'-pyrimidine]-5'-carbonitrile (**7**): Yellow powder, mp: 164 ºC. Yield 0.35 g, 75%. IR (KBr): 2227, 1643, 1573, 1249, 991, 772, 601. ^{1}H NMR (300 MHz, acetone-d_6): δ 4.99 (2H, s,

CH_2), 7.43 (5H, m, CH), 7.79 (4H, s, CH). ^{13}C NMR (75 MHz, acetone-d_6): δ 50.7 (CH_2), 85.5 (C), 86.4 (CCl_3), 108.4 (C), 110.5 (CN), 122.7 (CH), 128.5 (CH), 129.0 (CH), 129.8 (CH), 133.3 (CH), 135.3 (C), 137.5 (C), 164.2 (C), 172.0 (C), 196.0 (C=O). MS (EI, 70 eV): *m/z* (%) = 210 (100), 182 (12), 155 (45), 127 (72), 105 (48), 91 (8), 83 (7), 77 (42). Anal. Calcd for $C_{21}H_{13}Cl_3N_4O_2$ (459.71): C, 54.87; H, 2.85; N, 12.19. Found: C, 55.08; H, 2.90; N, 12.26.

7. *X-Ray Crystal-Structure Determination of* ***6a***: Structure determination and refinement data: formula, $C_{22}H_{15}Cl_3N_4O_2$. C_3H_6O: M_r 531.81; triclinic, space group P-1, a = 9.062(1) Å, b = 10.210(1) Å, c = 14.622(2) Å, α = 81.29(1)°, β = 75.98(1)°, γ = 75.18(1)°; Z = 2, V = 1263.1(3) Å^3, D_{calc} = 1.398 mg/m^3, MoK_α radiation (0.71073 Å), T = 293(2) K; 5288 reflections collected on a Bruker P4 diffractometer, 4375 unique (Rint = 0.0212), 3302 unique reflections with I>2σ(I). All non-hydrogen atoms have been located by difference Fourier maps and refined anisotropically. All hydrogen atoms, except those of the amine nitrogen, have been placed on calculated positions and refined isotropically by using the riding model. The amine protons have been located by difference Fourier maps and refined isotropically. Final indices [I>2σ(I)]: R_1 = 0.0501, wR_2 = 0.1229, GOF = 1.153. The crystallographic data of **6a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-977644. Copies of the data can be obtained, free of charge, *via* the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44-1223-336033).

8. Burnett, A. M. N.; Johnson, C. K. Oak Ridge National Laboratory Report ORNL-6895, Oak Ridge National Laboratory: Tennessee, **1996**.