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RESEARCH LETTER

Straightforward solvent-free synthesis of new chiral benzene-1,3,5-tricarboxamides

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A new series of chiral benzene-1,3,5-tricarboxamides (BTAs) **3a–e** was prepared using the ecofriendly solvent-free approach, starting with benzene-1,3,5-tricarbonyl chloride **1** and appropriate optically pure primary amines **2a–e**. All the reactions occur in a short time with excellent yields (>90%). The structures of the compounds have been characterized by Fourier transform infrared spectroscopy (FT-IR), Proton nuclear magnetic resonance (1H NMR), Carbon 13 nuclear magnetic resonance (13C NMR), electron ionization mass spectrometry (EI-MS), and elemental analysis.

Keywords: solvent-free; chiral C₃-symmetric ligands; benzene-1,3,5-tricarboxamides

1. Introduction

The widespread use of chiral tripodal ligands and the extensive studies of these symmetric ligands are due to their particular selective coordinating capacity with metal ions (1–11), efficient molecular recognition of biologically important substrates (12–17) and as highly attractive building blocks for the formation of supramolecular architectures (18–26). In particular, tripodal ligands that are chiral and based on a benzene-1,3,5-tricarboxamide (BTA) moiety are very attractive in asymmetric catalysis involving transition metal ions (27) and gelation (28), but there are scarce reports on such chiral entities.

The general procedures for the preparation of BTAs include the reaction of benzene-1,3,5-tricarbonyl chloride (trimesic chloride) with primary amines in the presence of base, although direct functionalization of benzene-1,3,5-tricarboxylic acid with the appropriate amine by using suitable coupling agents is also frequently applied under conventional homogeneous conditions in the organic solvent (29–31). However, these methods involve the use of volatile organic solvents and display only moderate-to-low yields.

On the other hand, in recent years, considerable attention has been paid to reactions done under the solvent-free approach (32, 33) because of the increasing concern of the harmful effects of organic solvents

on the environment and human health, and then organic reactions that are operated with green solvents or without conventional organic solvents have aroused great attention. In this regard, for reasons of economy and pollution prevention, along with mild reaction conditions, high efficiency and selectivity, easy separation and purification, the solvent-free approach is becoming more popular, and it is often claimed that the best solvent is no solvent (33–35).

Herein we would like to report the greener synthesis of five chiral BTAs **3a–e** in solvent-free conditions. The synthesis of such chiral BTAs results in good-to-excellent yields (>90%) in about 10 minutes, and it is worth noting to underline the preparation of such entities in a single and straightforward step under mild conditions.

2. Results and discussion

Reactions were carried out by mixing benzene-1,3,5-tricarbonyl chloride **1** with optically pure primary amines **2a–e** under solvent-free conditions at room temperature (Scheme 1). Reactants were mixed vigorously for 5–10 min in a round-bottom flask, observing the detachment of HCl as gas, depending of the agitation rate, which is crucial in the reaction, given that a fast agitation impedes a solid formation in the

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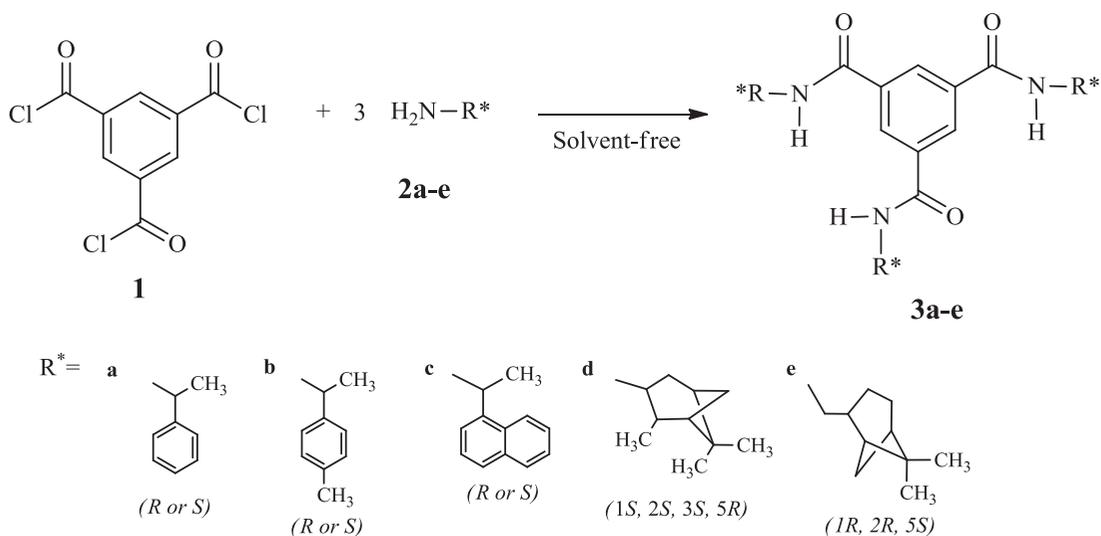
flask, and the HCl formed can be released yielding oily products that become solids standing on air in minutes. On the contrary, a slow agitation speed is induced in a clumsy solid because the HCl cannot be released to the surroundings reacting with another equivalent of amine to form the expected salt. The HCl detached in the flask can be easily trapped in a NaOH solution. Therefore, as it was mentioned earlier, the speed in the agitation is extremely significant and the reagents need to be mixed vigorously. The reaction was monitored by thin-layer chromatography, observing the disappearance of the reagents and the comparison with residual carboxylic acids as possible by-products was easily checked, confirming the absence of such by-products. Due to direct interaction and because no excess of reagents were used, the products were obtained with no waste and no further purification processes were needed. In most cases, the products were obtained in enough pure form, or a simple crystallization was enough, when necessary. As far as we are aware, the preparation of chiral BTAs **3a–e** has not been reported by using the solvent-free approach.

The couplings between acyl chlorides and some chiral amines were also examined by using different conditions, as mentioned in the literature (30, 31) but, as expected, the advantage of just mixing the reagents to afford almost instantly the product address this procedure as an excellent choice, compared with the methods currently available. The synthesis of BTA **3a** was previously reported using organic solvent as a reaction medium in 78% yield (36). All the synthesized compounds were characterized by routine techniques.

The Fourier transform infrared spectroscopy (FT-IR) absorption spectrum for compounds **3a–e** shows characteristic broad absorption band of the N–H stretching vibrations in the region of 3277–3222 cm^{-1} . The C=O stretching band in the region of 1645–1635 cm^{-1} , along with an absorption band in the region of 1562–1549 cm^{-1} corresponding to the N–H bending. Molecular ion peaks were observed for all the compounds in the mass spectrum, matching the expected molecular weights.

Compounds **3a–c** have similar Proton nuclear magnetic resonance (^1H NMR) spectra in $\text{DMSO-}d_6/\text{CDCl}_3$. A characteristic feature of the ^1H spectra for **3a**, **3b**, and **3c** is the amide proton resonance at 8.62, 8.55, and 8.73 ppm, respectively, as a multiplet, along with the signal assigned to the aromatic protons of benzene-1,3,5-tricarbonyl group which appeared as multiplet centered at 9.25, 9.28, and 9.24 ppm, respectively. The methyne protons appeared as two triplets about 5.19–5.15 and 4.37–4.32 ppm for compound **3a** and **3b**, respectively, with the same J_{HH} coupling constant of 6.6 Hz for each signal (methyne proton appeared normally as quadruplet in the optically active primary amine). For compound **3c**, the methyne protons appeared as two triplets centered at 6.00 and 5.30 ppm. In compound **3c**, the triplets are shifted downfield approximately at 0.9 ppm with respect to compounds **3a** and **3b**.

The ^1H NMR spectrum of compound **3d** and **3e** in $\text{DMSO-}d_6/\text{CDCl}_3$ showed the amide proton as a multiplet at 8.54 and 8.34 ppm, respectively, along with the aromatic protons of benzene 1,3,5-tricarbonyl group as multiplet centered at 9.32 and 9.25 ppm, respectively. The methyl protons for the quaternary carbon atoms of compound **3d** were observed as three



Scheme 1. Synthesis of chiral BTAs **3a–e** derived from benzene-1,3,5-tricarbonyl chloride and optically pure primary amines.

singlets at 1.28, 1.25, and 1.23 ppm ascribed to the isopinocampheyl moiety. For compound **3e**, methyl protons appeared as two singlets at 1.20 and 0.99 ppm.

3. Experimental section

3.1. General

¹H NMR and Carbon 13 nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian Mercury-400 with software VNMR 6.1 and a Jeol GX 400, using DMSO-*d*₆ and CDCl₃ as solvents and tetramethylsilane (TMS) as internal reference. Solutions of DMSO-*d*₆ and CDCl₃ in different ratios (30:70 for compounds **3a–c** and 50:50 for compounds **3d–e**) were prepared by mixing the two solvents directly in a sample tube. IR spectra were performed on a Nicolet FT-IR Magna 700 spectrometer with KBr disks. The electronic impact (EI) ionization mass spectra were acquired on a Jeol JMS-SX 102A mass spectrometer operated in the positive ion mode. The acquisition conditions were ion source temperature 230°C, ionization energy 70 eV, emission current 0.14 μA, and ionization current 100 μA. Melting points were measured using a Mel-Temp II apparatus and are uncorrected. The optical rotation was obtained on a Perkin Elmer 241 polarimeter. Elemental analyses were recorded from a Euro EA elemental analyzer. All reagents were purchased from Aldrich and used without further purification.

3.2. General procedure for preparation of compounds (3a–e).

A mixture of benzene-1,3,5-tricarbonyl trichloride (1 mmol) and 3 mmol of optically active primary amine (**2a–e**) was prepared thoroughly at room temperature under solvent-free conditions. The reaction was monitored by thin-layer chromatography. After the reaction was completed (5–10 min), the resultant white solid was filtered and washed with hexane and Et₂O, and allowed to dry in air to give **3a–e** in 93–96% yields.

3.2.1. (*R*)- or (*S*)-*N*¹,*N*³,*N*⁵-tris-[(1-phenyl)ethyl]-BTA (**3a**)

White solid, yield 95%, m.p. >360°C; [α]₂₅^D = −92.3 (*R,R,R*), +92.1 (*S,S,S*) (c = 1, DMSO); IR (ν_{max}, cm^{−1}): 3223, 1722, 1639 (C=O), 1552, 1282; ¹H NMR (400 MHz, DMSO-*d*₆-CDCl₃, 30:70) δ_H: 1.52 (d, 9H, ³J = 6.6 Hz, H₃C–CH), 4.37 (t, 2H, ³J = 6.6 Hz, HC–CH₃), 5.19 (t, 1H, ³J = 6.6 Hz, HC–CH₃), 7.51–7.27 (m, 15H, Ar), 9.25 (m, 3H, Ar), 8.62 (m, 3H, H–N); ¹³C NMR (400 MHz, DMSO-*d*₆-CDCl₃) δ_C: 21.03

(H₃C–CH), 50.27 (HC–CH₃), 127.05, 128.90, 129.21, 134.94, 139.61, 145.18 (Ar), 164.91 (C=O); EI-MS *m/z* (%): 120 (100) [M–C₂₆H₂₇N₂O₂]⁺; Anal. Calcd. for C₃₃H₃₃N₃O₃ (519.2): C 76.28, H 6.40; found C 76.03, H 6.21.

3.2.2. (*R*)- or (*S*)-*N*¹,*N*³,*N*⁵-tris-[1-(4-methylphenyl)ethyl]-BTA (**3b**)

White solid, yield 96%, m.p. 250–252°C; [α]₂₅^D = −24.7 (*R,R,R*), +24.6 (*S,S,S*) (c = 1, DMSO); IR (ν_{max}, cm^{−1}): 3222, 1720, 1639 (C=O), 1549, 1288 cm^{−1}; ¹H NMR (400 MHz, DMSO-*d*₆-CDCl₃, 30:70) δ_H: 1.51 (d, 9H, ³J = 6.6 Hz, H₃C–CH), 2.26 (s, 3H, H₃C–Ar), 2.30 (s, 6H, H₃C–Ar), 4.32 (t, 2H, ³J = 6.6 Hz, HC–CH₃), 5.15 (t, 1H, ³J = 6.6 Hz, HC–CH₃), 7.41–7.10 (AA 'BB' system, 12H, Ar), 9.28 (m, 3H, Ar), 8.55 (m, 3H, H–N); ¹³C NMR (400 MHz, DMSO-*d*₆-CDCl₃) δ_C: 20.96 (H₃C–CH), 22.50 (H₃C–Ar), 50.04 (HC–CH₃), 128.97, 129.43, 135.85, 136.69, 137.96, 142.12 (Ar), 164.92 (C=O); EI-MS *m/z* (%): 105 (100) [M–C₂₉H₃₄N₃O₂]⁺; Anal. Calcd. for C₃₆H₃₉N₃O₃ (561.3): C 76.98, H 7.00; found C 76.93, H 6.95.

3.2.3. (*R*)- or (*S*)-*N*¹,*N*³,*N*⁵-tris-[1-(1-naphthyl)ethyl]-BTA (**3c**)

White solid, yield 95%, m.p. >360°C; [α]₂₅^D = −40.3 (*R,R,R*), +40.2 (*S,S,S*) (c = 1, DMSO); IR (ν_{max}, cm^{−1}): 3277, 1635, 1633 (C=O), 1562, 1251 cm^{−1}; ¹H NMR (400 MHz, DMSO-*d*₆-CDCl₃, 30:70) δ_H: 1.81 (d, 9H, ³J = 6.6 Hz, H₃C–CH), 5.30 (t, 2H, ³J = 6.6 Hz, HC–CH₃), 6.00 (t, 1H, ³J = 6.6 Hz, HC–CH₃), 7.96–7.43 (m, 21H, Ar), 8.73 (m, 3H, H–N), 9.24 (m, 3H, Ar); ¹³C NMR (400 MHz, DMSO-*d*₆-CDCl₃) δ_C: 21.05 (H₃C–CH), 47.18 (HC–CH₃), 125.45, 126.01, 126.95, 128.77, 129.13, 133.65, 134.02, 138.36, 143.89 (Ar), 165.95 (C=O); EI-MS *m/z* (%): 155 (100) [M–C₃₃H₂₈N₃O₃]⁺; Anal. Calcd. for C₄₅H₃₉N₃O₃ (669.3): C 80.69, H 5.87; found C 80.63, H 5.90.

3.2.4. *N*¹,*N*³,*N*⁵-tris-[(1*S*,2*S*,3*S*,5*R*)-(+)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl]-BTA (**3d**)

White solid, yield 95%, m.p. >360°C; [α]₂₅^D = +21.4 (c 1, CH₃OH/CHCl₃); IR (ν_{max}, cm^{−1}): 3233, 1723, 1645 (C=O), 1559, 1277 cm^{−1}; ¹H NMR (400 MHz, DMSO-*d*₆-CDCl₃, 50:50) δ_H: 0.95 (s, 9H, H₃C–CH), 1.23 (s, 6H, (H₃C)₂-C), 1.25 (s, 6H, (H₃C)₂-C), 1.28 (s, 6H, (H₃C)₂-C), 1.84 (m, 3H, HC–CH₃), 2.0 (m, 6H, H₂C–CH), 2.24 (m, 6H, H₂C–CH), 2.42 (m, 3H, HC), 2.57 (m, 3H, HC), 3.54 (m, 3H, HC–N), 8.54 (m, 3H, H–N), 9.32 (m, 3H, Ar); ¹³C NMR (400 MHz, DMSO-*d*₆-CDCl₃) δ_C: 20.62 (H₃C–CH), 23.40 (H₃C–

C), 27.65 (H₃C–C), 33.64 (CH₂), 34.07 (CH₂), 38.51 (C–(CH₃)₂), 41.05 (CH), 42.56 (CH), 47.44 (CH), 50.69 (HC–N), 128.72, 133.45 (Ar), 161.77 (C=O); EI-MS *m/z* (%): 328 (100) [M–C₁₉H₂₉NO]⁺; Anal. Calcd. for C₃₉H₅₇N₃O₃ (615.44): C 76.06, H 9.33; found C 76.11, H 9.28.

3.2.5. *N*¹,*N*³,*N*⁵-tris-[(–)-2-{(1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-yl}methyl]-benzene-1,3,5-tricarboxamide (*3e*)

White solid, yield 96%, m.p. 190–191°C (decomposed); [α]_D²⁵ = –15.2 (c 1, CH₃OH/CHCl₃); IR (ν_{max}, cm^{–1}): 3225, 1726, 1639 (C=O), 1559, 1274 cm^{–1}; ¹H NMR (400 MHz, DMSO-*d*₆-CDCl₃, 50:50): δ_H: 0.99 (s, 9H, H₃C–C), 1.20 (s, 9H, H₃C–C), 2.02–1.55 (m, 24H, CH₂), 2.55–2.33 (m, 6H, HC), 3.43 (m, 3H, HC), 8.34 (m, 3H, H–N), 9.25 (m, 3H, Ar); ¹³C NMR (400 MHz, DMSO-*d*₆-CDCl₃) δ_C: 19.22 (H₃C–C), 22.67 (H₃C–C), 25.34 (CH₂), 27.36 (CH₂), 32.55 (CH₂), 38.37 (CH), 39.53 (CH), 40.85 (CH), 43.23 (C–(CH₃)₂), 45.33 (H₂C–N), 128.34, 135.11 (Ar), 165.94 (C=O). EI-MS *m/z* (%): 193 (100) [M–C₂₇H₃₈N₂O₂]⁺; Anal. Calcd. for C₃₉H₅₇N₃O₃ (615.44): C 76.06, H 9.33; found C 75.97, H 9.38.

4. Conclusions

In summary, we have described a simple and efficient procedure for the synthesis of chiral C₃-symmetric BTAs **3a–e** in solvent-free conditions by just mixing the reagents at room temperature. To our knowledge, chiral BTA **3a** was previously reported by solvent conditions with yield less than 80%, and **3b–e** are all new compounds (yield >90%), all obtained in less than 10 minutes. The present protocol has several advantages, particularly solvent-free conditions, fast reaction times, high yields, and ecofriendly operational and experimental simplicity along with very mild conditions. Overall, this versatile approach can be applied to the synthesis of a range of chiral and achiral benzene-1,3,5-tricarboxamide.

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