New domino reaction for the selective synthesis of tetracyclic cinnolino[5,4,3-*cde*]cinnolines†

Bo Jiang,[a,b] Wen-Juan Hao,[a] Jin-Peng Zhang,[c] Shu-Jiang Tu*[a,b] and Feng Shi[a]

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A new domino reaction for the highly selective synthesis of tetracyclic cinnolino[5,4,3-*cde*]cinnolines using steric control was described. In this reaction, the use of anthenes with aliphatic groups (R_1) leads to cinnolino[5,4,3-*cde*]cinnolines whereas anthenes with aryl groups (R_1) result in *N*-amino-1,8-dioxoacridines.

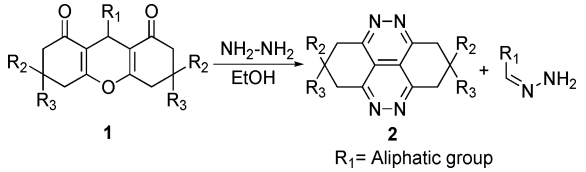
Introduction

The creation of molecular complexity and diversity from simple substrates, with simultaneous consideration of the economic and environmental aspects, constitutes a great challenge in modern organic chemistry, both from academic and industrial points of view. In this context domino reactions have proven to be very effective and attractive.[1] The notable feature of a domino process is that bonds and new functionalities are constructed that, in turn, react further under identical conditions to form new bonds and functionalities, until termination leads to a stable final product. Clearly, the usefulness of a domino reaction depends on the number of bonds formed and the complexity of the product. The amounts of solvents, reagents, absorbents and energy used in domino reactions has the potential to be much lower than for conventional stepwise approaches, which can be laborious, as well as generating several equivalents of waste and salt as by-products. Hence, environmentally benign and atom-economic domino processes[2] that create complex compounds can play an important role in organic synthesis, especially when the products are chemically significant and synthetically challenging, as is the case for tetracyclic cinnolino[5,4,3-*cde*]cinnolines.

Six-membered nitrogen-containing heterocycles are present in numerous natural products that exhibit important biological properties. For example, cinnolines and their derivatives are widely used as agrochemical and pharmaceutical drugs,[3] and they can act as microbicides,[3a] pollen suppressants,[3b–d] fungicides[3e] and herbicides,[3f,g] as well as bactericides in the pharmaceutical industry.[4] The chemistry of cinnolines has therefore received much attention.

The reaction of hydrazine hydrate with 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione has been reported to give 2,2,7,7-tetramethyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**2a**) and 1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (**2b**), respectively.[5] The reaction went to completion at 0–5 °C after 6 hours, but gave a maximum yield of only ~27%. Stille and co-workers found that the formation of polymeric compounds is the major side-reaction responsible for the poor chemical yield.[5a] Since then, many efforts on inhibiting polymer formation have been made, but have not been very successful so far.

As part of our continued interest in the development of highly efficient methods for the construction of important heterocyclic skeletons,[6] we are pleased to find that treatment of 1,8-dioxo-2,3,4,5,6,7-hexahydroanthenes with hydrazine hydrate can selectively lead to cinnolino[5,4,3-*cde*]cinnolines with good to excellent yield (Scheme 1). This paper reports our findings.



Scheme 1

Results and discussion

1,8-Dioxo-2,3,4,5,6,7-hexahydroanthenes are versatile and readily obtainable reagents, and their chemistry has received considerable attention in recent years.[7] Our strategy of synthesizing the anthenes **1** was through the reaction of aldehydes with cyclic 1,3-diketones. Various representative aldehydes (aliphatic: propionaldehyde, pentanal, 2-phenylacetaldehyde, *etc.*; aromatic: 4-bromo-, 4-chloro-, 4-fluoro-, and 4-methylbenzaldehyde; heteroaromatic: thiophene-2-carbaldehyde; α,β-unsaturated aromatic: cinnamaldehyde) were selected for our study.[8] To our satisfaction, the reaction of 1,8-dioxo-2,3,4,5,6,7-hexahydroanthenes with hydrazine hydrate selectively resulted in cinnolino[5,4,3-*cde*]cinnolines in good to excellent yields. Initially, several solvents (including toluene, THF, DMF and ethanol) were used at various temperatures (60–90 °C), but incomplete reaction was observed in toluene, THF and DMF. However, we found that by simply refluxing a solution of the two reactants in ethanol for 3–7 h and then cooling the reaction solution to room temperature resulted

[a]*School of Chemistry and Chemical Engineering, Xuzhou Normal University, Jiangsu, P.R. China. E-mail: laotu@xznu.edu.cn; Fax: +86 (516) 83500065; Tel: +86 (516) 83500065*
[b]*College of Chemistry, Chemical Engineering and Materials Science, Suzhou University, Suzhou, P.R. China*
[c]*Department of Public Health, Xuzhou Medical College, Xuzhou, 221000, People's Republic of China*

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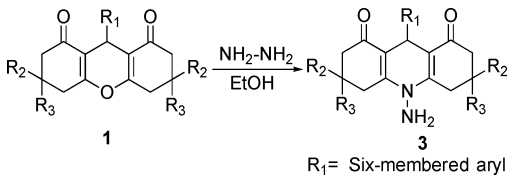
in precipitation of tetracyclic cinnolino[5,4,3-*cde*]cinnolines **2**. Obviously, the use of ethanol as the solvent under these conditions inhibits the formation of polymeric side-products.

We next explored the scope of this reaction using various R_1-substituted 1,8-dioxo-2,3,4,5,6,7-hexahydroanthenes **1** containing aliphatic and aromatic groups. When R_1 was aliphatic, the cinnolino[5,4,3-*cde*]cinnolines **2** were obtained in high yields (57–89%). When R_1 was a six-membered aryl group, *N*-aminoacridinediones **3** were produced in high yields (86–92%) (Scheme 2). It should be pointed out *N*-aminoacridinediones are new compounds except for **3a** and **3b**,[9] which were synthesized for the first time using our method. Importantly, 1,4-dihydropyridines (1,4-DHPs) have become major derivatives for the treatment of cardiovascular disorders due to their ability to inhibit Ca^{2+} entry into the cells of cardiac and vascular muscle.[10] With their 1,4-DHP nucleus, acridinediones have showed a diverse range of biological properties,[11] and so synthetic *N*-aminoacridinediones containing the acridine skeleton and 1,4-dihydropyridine (1,4-DHP) units could be interesting compounds for biological and physical research.

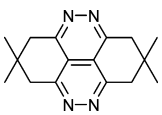
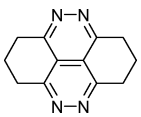
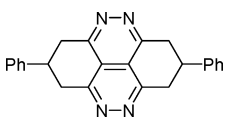
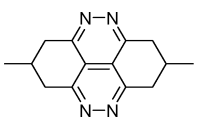
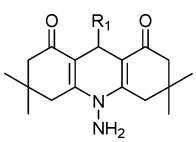


Scheme 2

The results were listed in Table 1. During the process of synthesizing compounds **2**, we observed interesting steric effects: substituents (R_1) with short alkyl straight-chains gave a faster reaction rate and provided higher yields (Table 1, entry 7). In contrast, substitutions with longer alkyl chains (R_1) (Table 1, entry 3) on the 1,8-dioxoanthene ring led to slower reactions. Benzyl, styryl, *t*-butyl, *i*-butyl, and thiophen-2-yl substituents also yielded cinnolino[5,4,3-*cde*]cinnolines (Table 1, entries 1, 2, 4, 5, and 8). As shown in Table 1, the yields of products **2** were significantly improved compared to the yields in the literature (<27%).[5] In addition, all substrates **1**, with both electron-donating groups and electron-withdrawing groups, can all be used for this reaction, and can then lead to *N*-aminoacridinediones **3** in excellent yields.

As shown in Table 1, two types of heterocycles have been selectively synthesized by using substrates with various substituents

Table 1 Synthesis of compounds **2** and **3**

Entry	Product		R_1	R_2	R_3	Time/h	Yield/%[a]	Mp/°C
1	**2a**		Bn	Me	Me	6.0	76 (25)[5a]	289–290
2			Styryl	Me	Me	4.5	73	—
3			*n*-Butyl	Me	Me	4.5	79	—
4			*i*-Butyl	Me	Me	5.0	68	—
5			*t*-Butyl	Me	Me	6.0	57	—
6			*n*-Pr	Me	Me	3.5	83	—
7			Et	Me	Me	3.0	88	—
8			Thiophen-2-yl	Me	Me	5.0	64	—
9	**2b**		Et	H	H	3.5	84 (27)[5a]	270–271
10	**2c**		Et	H	Ph	3.5	85 (22)[5b]	> 300
11	**2d**		Et	H	Me	4	89	> 300
12	**3a**		4-Bromophenyl	Me	Me	1	92	222–223
13	**3b**		4-Chlorophenyl	Me	Me	1.5	89	>300
14	**3c**		4-Fluorophenyl	Me	Me	1.2	90	>300
15	**3d**		4-Tolyl	Me	Me	1.5	86	290–291

[a] Isolated yields.

(R_1). In particular, the reaction of 1,8-dioxoanthenes **1** (R_1 = aliphatic group) with hydrazine hydrate can occur without using any catalysts; this led to the formation of a fused tetracyclic system **2** with two pyridazine rings and two cyclohexane units. During this cascade process, two carbon–oxygen and two carbon–carbon bonds of the pyran ring were cleaved. At the same time, up to five new σ bonds and four carbon–nitrogen bonds can be formed. It should be noted that this reaction can be performed on a multigram scale under the simple conditions described above.

Proposed reaction mechanism

A proposed mechanism is outlined in Scheme 3. Initially, due to the two strongly electron-withdrawing groups at the α- positions of the anthenes **1**, an S_NV (nucleophilic vinylic substitution)-type reaction[12] occurs when one of the amino groups of hydrazine attacks a vinylic carbon atom of anthenes; this leads to open chain enamine intermediate **A**, which cyclizes to generate unstable and easily decomposed diazepine **B**. This intermediate then undergoes [3,3]-sigmatropic rearrangement[13] to afford the cyclopropane intermediate **C**, which is intercepted by hydrazine to give pyridazine **D**. This then undergoes elimination catalyzed by hydrazine to yield methylene-hydrazine and intermediate **E**. This then reacts with hydrazine to give the aromatized cinnolino[5,4,3-*cde*]cinnoline **2** by dehydrogenation. In addition, the open-chain intermediate **A** can undergo intramolecular cyclization to yield a stable 1,4-dihydropyridine (1,4-DHP) intermediate. We reasoned that such a divergence in reaction paths is caused by the resistance of intermediate **B** to [3,3]-sigmatropic rearrangement, because this would generate a sterically crowded aryl system and result in a repulsive interaction between the π-electrons of the aryl and carbonyl groups – in addition, the two carbonyl groups of intermediate **B** are closer than in acridinediones **3**. Furthermore, due to the closer distance between the two carbonyl groups, the repulsive interaction between the π-electrons of the aryl and carbonyl groups strengthens dramatically; this leads to resistance of intermediate **B** to [3,3]-sigmatropic rearrangement. Therefore, in general, the combined action of these two factors will make the reaction selective.

The new products were characterized by IR, NMR, and HRMS. Furthermore, the structures of **2a**, **2b**, and **3a** were further confirmed by single-crystal X-ray analysis (Fig. 1–3).

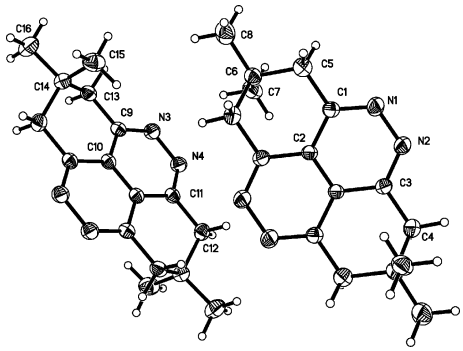


Fig. 1 ORTEP drawing of **2a**.

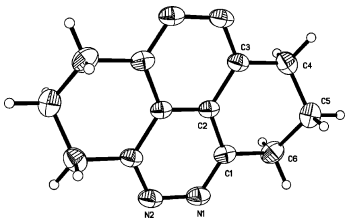
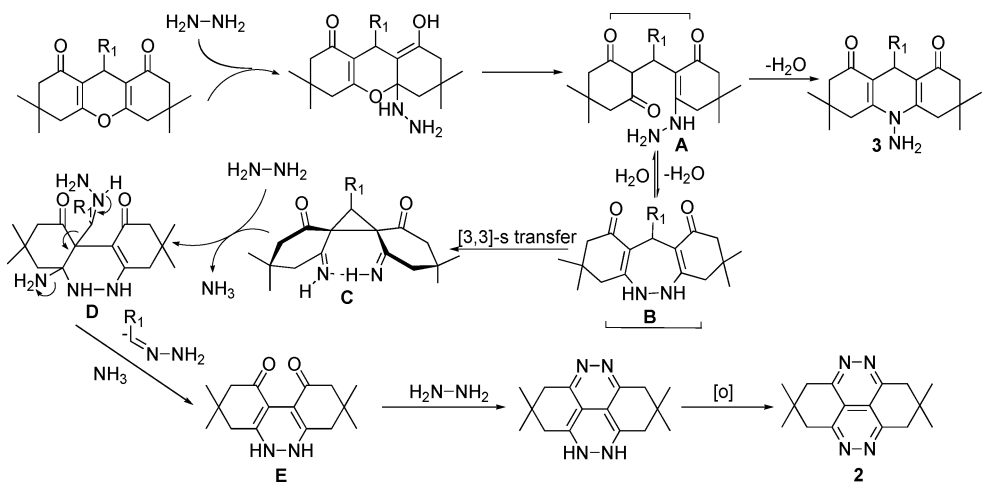


Fig. 2 ORTEP drawing of **2b**.

Conclusion

In summary, a novel, highly selective, efficient and catalyst-free domino reaction of 1,8-dioxoanthenes **1** with hydrazine hydrate has been developed, giving rise to unusual tetracyclic cinnolino[5,4,3-*cde*]cinnolines. The reaction is easy to perform using inexpensive starting materials under simple conditions to give high yields and chemoselectivity. A reasonable mechanism has been proposed which involves many steps in a one-pot operation, such as the ring-closure cascade, an S_NV step, a [3,3]-sigmatropic rearrangement, nucleophilic addition, nucleophilic



Scheme 3

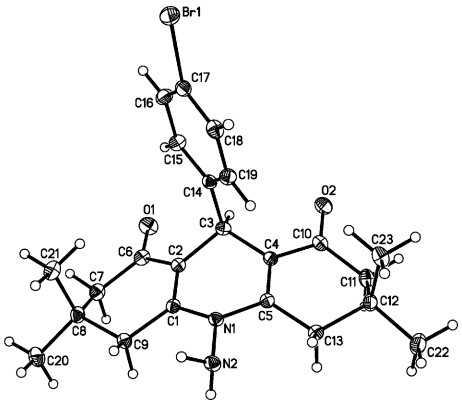


Fig. 3 ORTEP drawing of **3a**.

substitution and aromatization. It is expected that this reaction will find application in the total synthesis of complex products of biomedical importance.

Experimental

General

Melting points were determined in open capillaries and were uncorrected. ^{1}H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 400 (100) MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. The exact mass measurements were obtained by high resolution mass instrument (GCT-TOF instrument). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

General procedure for the synthesis of 2

In a 50-mL flask, 3,4,6,7-tetrahydro-3,3,6,6,9-pentamethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (2 mmol), hydrazine hydrate 80% (8 mmol), and ethanol (8 mL) were mixed with magnetic stirring at 80 °C until the disappearance of starting material was confirmed by TLC. Upon completion, the reaction mixture was cooled to room temperature. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude products were purified by flash chromatography (silica gel, petroleum ether–acetone = 10:1) to give the pure product **2a**.

2,2,7,7-Tetramethyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]-cinnoline (2a). A pale yellow solid (known compound).[5a] IR (KBr, ν, cm^{-1}): 1514, 1467, 1388, 1369, 1319, 1291, 1254, 1165, 1129, 931, 827. ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 3.16 (s, 8H, CH_2), 1.08 (s, 12H, CH_3).

1,2,3,6,7,8-Hexahydrocinnolino[5,4,3-*cde*]cinnoline (2b). A pale yellow solid (known compound).[5a] IR (KBr, ν, cm^{-1}): 1543, 1516, 1390, 1360, 1290, 1267, 1167, 981. ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 3.31–3.27 (m, 8H, CH_2), 2.28–2.22 (m, 4H, CH_2).

2,7-Diphenyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (2c). A colorless solid (known compound).[5b] IR (KBr, ν, cm^{-1}):1604, 1533, 1510, 1380, 1350, 1240, 1217, 1167, 991. ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 7.50 (d, J = 7.6 Hz, 4H, ArH), 7.41 (t, J = 7.6 Hz, 4H, ArH), 7.31 (t, J = 6.8 Hz, 2H, ArH), 3.67–3.51 (m, 8H, CH_2), 3.31–3.28 (m, 2H, CH).

2,7-Dimethyl-1,2,3,6,7,8-hexahydrocinnolino[5,4,3-*cde*]cinnoline (2d). A colorless solid. IR (KBr, ν, cm^{-1}): 1553, 1516, 1390, 1370, 1250, 1227, 1147, 981 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm): 3.36-3.31 (m, 6H, CH_2), 3.04-2.97 (m, 4H, CH and CH_2), 1.23 (d, 6H, J = 6.8 Hz, 2CH_3). HRMS (ESI): m/z calcd for: 240.1375, found: 240.1371.

Byproduct: Thien-2-ylmethylene-hydrazine. A yellow solid (known compound);[14] m.p. 66–67 °C; MS (EI) [M$^+$]: 126.

Preparation of compounds 3

In a 50-mL flask, 9-(4-bromophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8 (5*H*,9*H*)-dione (2 mmol), hydrazine hydrate 80% (3 mmol), and ethanol (8 mL) were mixed with magnetic stirring at 80 °C until the disappearance of starting material was confirmed by TLC. Upon completion, the reaction mixture was cooled to room temperature. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude products were purified by flash chromatography (silica gel, petroleum ether–acetone = 10:1) to give the pure product **3a**.

***N*-Amino-9-(4-bromophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*,9*H*,10H)-dione (3a).** A light yellow solid. IR (KBr, ν, cm^{-1}): 3350, 2954, 1626, 1561, 1487, 1219, 1009, 882, 769. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 2H, ArH), 5.30 (s, 2H, NH_2), 4.91 (s, 1H, CH), 2.90 (d, J = 18.0 Hz, 2H, CH_2), 2.53 (d, J = 18.0 Hz, 2H, CH_2), 2.19 (d, J = 16.0 Hz, 2H, CH_2), 2.01 (d, J = 16.0 Hz, 2H, CH_2), 1.03 (s, 6H, 2CH_3), 0.86 (s, 6H, 2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 194.5, 154.8, 145.9, 130.5, 129.7, 118.5, 110.7, 49.5, 31.5, 31.4, 29.4, 26.7. HRMS (ESI): m/z calcd for: 442.1256, found: 442.1242.

***N*-Amino-9-(4-chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*, 9*H*,10*H*)-dione (3b).** A light yellow solid. IR (KBr, ν, cm^{-1}): 3337, 2958, 1630, 1488, 1319, 1143, 979, 886. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.22 (d, J = 8.4 Hz, 2H, ArH), 7.15 (d, J = 8.4 Hz, 2H, ArH), 5.30 (s, 2H, NH_2), 4.92 (s, 1H, CH), 2.89 (d, J = 18.0 Hz, 2H, CH_2), 2.51 (d, J = 15.6 Hz, 2H, CH_2), 2.16 (d, J = 16.0 Hz, 2H, CH_2), 2.01 (d, J = 16.0 Hz, 2H, CH_2), 1.03 (s, 6H, 2CH_3), 0.85 (s, 6H, 2CH_3). HRMS (ESI): m/z calcd for: 398.1761, found: 398.1780.

***N*-Amino-9-(4-fluorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*, 9*H*,10*H*)-dione (3c).** A light yellow solid. IR (KBr, ν, cm^{-1}): 3339, 3055, 2958, 1626, 1566, 1321, 1126, 975, 883.^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.15 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 2H, ArH), 6.97 (t, J = 8.8 Hz, 2H, ArH), 5.30 (s, 2H, NH_2), 4.94 (s, 1H, CH), 2.89 (d, J = 14.0 Hz, 2H, CH_2), 2.53 (d, J = 14.0 Hz, 2H, CH_2), 2.17 (d, J = 15.6 Hz, 2H, CH_2), 2.02 (d, J = 16.0 Hz, 2H, CH_2), 1.03 (s, 6H, 2CH_3), 0.86 (s, 6H, 2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 194.6, 154.6, 129.0, 128.9, 114.3, 114.1, 111.0, 49.5, 31.5, 30.9, 29.5, 26.7. HRMS (ESI): m/z calcd for: 382.2057, found: 382.2061.

***N*-Amino-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (3d).** A light yellow solid. IR (KBr, ν, cm^{-1}): 3343, 2960, 1632, 1565, 1469, 1143, 887, 714. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.02 (d, J = 8.0 Hz, 2H, ArH),

6.94 (d, J = 8.0 Hz, 2H, ArH), 5.29 (s, 2H, NH_2), 4.90 (s, 1H, CH), 2.88 (d, J = 14.0 Hz, 2H, CH_2), 2.51 (d, J = 14.0 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.15 (d, J = 16.0 Hz, 2H, CH_2), 1.99 (d, J = 16.0 Hz, 2H, CH_2), 1.02 (s, 6H, $2CH_3$), 0.86 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 194.5, 154.4, 143.6, 134.3, 128.2, 127.3, 112.7, 112.2, 49.6, 31.5, 31.0, 29.5, 26.7, 20.6. HRMS (ESI): m/z calcd for: 378.2307, found: 378.2308.

Determination of X-ray crystal structures

2a. Growth of a single crystal was carried out in ethanol at room temperature. Crystal data for $C_{16}H_{20}N_4$, M = 268.36, monoclinic, space group $P2_1/n$, a = 12.819(4), b = 8.441(3), c = 13.310(4), V = 1433.7(8) Å^3, Z = 4, T = 298(2) K, μ = 0.077 mm^{-1}, 7218 reflections measured, 2518 unique reflections, R = 0.0521, R_w = 0.1342. CCDC 695205.

2b. Growth of a single crystal was carried out in ethanol at room temperature. Crystal data for $C_{12}H_{12}N_4$, M = 212.26, monoclinic, space group $P2_1/c$, a = 9.698(5), b = 5.875(3), c = 10.023(5), V = 507.4(4) Å^3, Z = 2, T = 298(2) K, μ = 0.088 mm^{-1}, 2508 reflections measured, 890 unique reflections, R = 0.0410, R_w = 0.1007. CCDC 695206.

3a. Growth of a single crystal was carried out in ethanol at room temperature. Crystal data for $C_{23}H_{27}BrN_2O_2$, M = 443.38, orthorhombic, space group $Pbca$, a = 11.8053(10), b = 15.6404(15), c = 2.432(2), V = 4141.8(6) Å^3, Z = 8, T = 193(2) K, μ = 0. 2006 mm^{-1}, 43797 reflections measured, 4743 unique reflections, R = 0.0423, R_w = 0.0993.[9]

Acknowledgements

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