molbank

MDPI

Communication

Methyl 12-Methyl-3,9-dinitro-5,6,7,12-tetrahydro-13-oxodibenzo[*b*.*g*]bicyclo[3.3.1]nonane-6-carboxylate and Related Compounds

Dylan R. Nanney and Richard A. Bunce *

Department of Chemistry, Oklahoma State University, Stillwater, OK 74078-3071, USA
* Correspondence: rab@okstate.edu; Tel.: +1-405-744-5952

Abstract: A synthesis of the title compound and related structures is reported. The procedure involves double alkylation of a β-ketoester followed by double S_NAr ring closure from the γ carbon to give a dibenzo[3.3.1]bicyclic unit. This paper appears to be the first to generate a mid-sized bicyclic target by a double S_NAr process. The synthesis can be performed in one step, but yields are superior (52–62%) when a two-stage procedure is used.

Keywords: double alkylation; double S_NAr ring closure; dibenzo[3.3.1]bicyclic systems

Citation: Nanney, D.R.; Bunce, R.A. Methyl 12-Methyl-3,9-dinitro-5,6,7,12-tetrahydro-13-oxodibenzo[*b*.*g*]bicyclo[3.3.1]nonane-6-carboxylate and Related Compounds. *Molbank* **2022**, *2022*, M1526. https://doi.org/10.3390/M1526

Academic Editor: R. Alan Aitken

Received: 24 November 2022
Accepted: 9 December 2022
Published: 12 December 2022

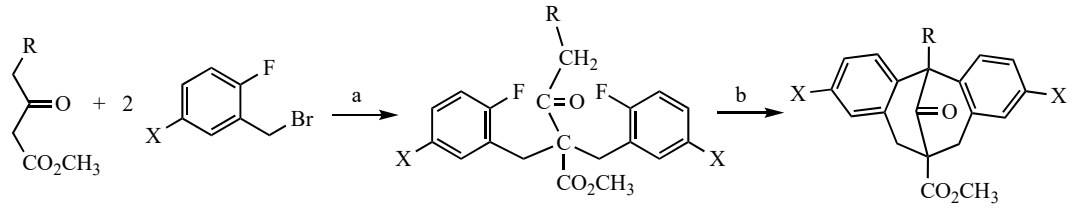
1. Introduction

The S_NAr reaction is an important tool in medicinal chemistry [1–3]. Generally, it is a method exploited to link heteroatoms and active methylene centers to aromatic rings. Often it is used to close ring systems in biologically relevant molecules, but its use to close multiple rings in a single operation is rare. One of the first reports of a double cyclization by S_NAr was the magnificent synthesis of ristocetin aglycon by Boger and co-workers [4]. Though the two ring-forming reactions were not merged into a single operation, this synthesis used an extremely mild application of this reaction for the construction of a complex macrocyclic antibiotic. A more recent example of double ring closure by S_NAr reactions included the assembly of several smaragdyrin derivatives by Jiao and co-workers [5]. Smaragdyrins are expanded heterocyclic porphyrins that are of interest structurally and for their "tunable" aromaticity and have also been employed as near infrared organic dyes, fluorescent probes, nonlinear optical materials, photosensors for photodynamic therapy and contrasting agents for magnetic resonance imaging [6]. In this report, a double S_NAr strategy was employed for the construction of several of these complex porphyrinoids for further evaluation in potential therapeutic applications. In a further study, Nakamura and co-workers disclosed a six-membered ring closure of two *o*-fluorodiarylamines in the presence of catalytic iron (II) chloride and stoichiometric 1,2-dibromoethane [7]. The targeted diaryl dihydrophenazines have attracted attention due to their significant magnetic properties [8] and demonstrated promise as luminescent materials [9] and photoredox catalysts [10]. Finally, Bunce and Grant communicated a double S_NAr procedure to close the central ring of several 9(10*H*)-acridinone derivatives [11]. This class of compounds is known to possess active biological profiles against bacteria, viruses, fungi and other parasites.

2. Results

In the current work, we describe a facile synthesis of methyl 12-methyl-3,9-dinitro-5,6,7,12-tetrahydro-13-oxodibenzo[*b*.*g*]bicyclo[3.3.1]nonane-6-carboxylate (**1a**) using a double alkylation-double S_NAr strategy (see Scheme 1). The transformation was noted as attempts were made to prepare substituted 4*H*-1-benzopyrans in DMF as it is a better solvent for both the alkylation and the S_NAr reaction than acetone used in the original report [12]. The conversion proceeded as a domino reaction using a 1:2:4 mol ratio of methyl propionylacetate

(**2a**): 2-fluoro-5-nitrobenzyl bromide (**3**) [12]: anhydrous potassium carbonate in dry DMF, but in only 20–25% yield. Performing the reaction as a two-step sequence, however, using a 1:2:2 mole ratio of the same reactants at 23 °C for 2 days gave the dialkylated ketoester **5** in 64% yield. Subsequent treatment of **5a** with 2 equiv of base at 75 °C for 1 h gave the bicyclic compound in 82% yield. Thus, an overall reproducible yield of 52% was achieved for the title compound and 53–62% for additional examples described in the Supplemental Materials. Bicyclic structure **1a** was isolated from the one-step domino procedure by preparative thin layer chromatography as a light yellow crystalline solid with a high melting point of 267–268 °C. The FT-IR indicated that the product had retained the ester functionality (C=O at 1739 cm^{-1}) and possessed a strained ketone carbonyl (C=O at 1732 cm^{-1}) as well as nitro absorptions (1350 and 1351 cm^{-1}). The ^{1}H-NMR presented only three types of aromatic protons between δ 8.16 and δ 7.79, a methyl ester at δ 3.78, two AB doublets at δ 3.90 and δ 3.52, and an aliphatic methyl at δ 1.89. Integration of the proton signals suggested the presence of two equivalent aromatic rings, one methyl ester, two equivalent diastereotopic methylenes and a single aliphatic methyl, for a total of 16 unique protons. The ^{13}C-NMR also revealed a very symmetrical structure with 2 carbonyls (δ 206.3—ketone and δ 171.5—ester), as well as 6 aromatic and 5 aliphatic signals for a total of 13 unique carbons. The interpretation of these data led to the dibenzo[3.3.1]bicyclic ketoester **1a**. Yields and physical data for **5a** and **1a** are summarized in Table 1.



2a-g **3** (X = NO_2) **4** (X = CN) **5a-g** **1a-g**

Scheme 1. Synthesis of substituted dibenzo[3.3.1]bicyclics. Key: (a) 2 equiv K_2CO_3, DMF 23 °C, 2 days; (b) 2 equiv K_2CO_3, 75 °C, 2 h. (X = NO_2: **1a**: R = CH_3, **1b**: R = CH_2CH_3, **1c**: R = $CH_2CH_2CH_3$, **1d:** R = CH_2Ph; X = CN: **1e**: R = CH_3, **1f**: R = $CH_2CH_2CH_3$, **1g**: R = CH_2Ph).

Table 1. Compounds prepared by double alkylation followed by double S_NAr. (Note: Spectral data for compounds **5a**–**g** and **1a**–**g** are in the Supplementary Materials).

			Compound 5		Compound 1	
Entry	**R**	**X**	**Yield (%)**	**m.p. (°C)**	**Yield (%)**	**m.p. (°C)**
a	CH_3	NO_2	64	112–114	82	267–268
b	CH_2CH_3	NO_2	77	83–84	81	238–239
c	$CH_2CH_2CH_2CH_3$	NO_2	64	96–98	87	209–210
d	CH_2Ph	NO_2	65	151–152	85	240–241
e	CH_3	CN	82	103–104	72	243–245
f	$CH_2CH_2CH_2CH_3$	CN	65	oil	82	190–191
g	CH_2Ph	CN	80	120–121	74	272–274

Various other derivatives having ethyl, butyl and benzyl in place of the bridgehead methyl have been prepared using the same two-step procedure (see Table 1). The intermediate dialkylated ketoesters and final bicyclic products for the analogs prepared are all characterized in the Supplementary Materials. Additionally, derivatives incorporating a C5 cyano group on the S_NAr accepting ring with methyl, butyl and benzyl bridgehead alkyl groups are also reported. The overall sequence appears to be general for substrates possessing two sets of enolizable protons α and γ to the ester. Among the substrates reacted, the only exception to this observation was for methyl 4-phenyl-3-oxobutanoate, where the phenyl promotes competitive initial alkylation by the benzylic halide at the γ carbon.

This appears to be the first report of a relatively small bicyclic structure constructed by a double S_NAr process. Further work is currently being explored to evaluate the use of this protocol for the synthesis of heterocyclic ring systems.

3. Materials and Methods

3.1. General Methods

All reagents and solvents were used as received. Unless otherwise indicated, all reactions were performed under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC) on Analtech No 21521 silica gel GF plates (Newark, DE, USA). Preparative thin layer chromatography (PTLC) was performed using Analtech No 02015 silica gel GF plates (Newark, DE, USA). Band elution for all chromatographic separations was monitored using a hand-held UV lamp (Fisher Scientific, Pittsburgh, PA, USA). Melting points were obtained using a MEL-TEMP apparatus (Cambridge, MA, USA) and are uncorrected. FT-IR spectra were run as thin films on NaCl disks using a Nicolet iS50 spectrophotometer (Madison WI, USA). ^{1}H- and ^{13}C-NMR spectra were measured using a Bruker Avance 400 system (Billerica, MA, USA) at 400 MHz and 101 MHz, respectively, in the indicated solvents containing 0.05% of $(CH_3)_4Si$ as the internal standard; coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS-ESI) were obtained using a Thermo LTQ-Orbitrap XL mass spectrometer (Thermo Scientific, Waltham, MA, USA). Elemental analysis (±0.4%) on the title compound was determined by Atlantic Microlabs (Norcross, GA, USA).

*3.2. Example Procedure: Methyl 12-Methyl-3,9-dinitro-5,6,7,12-tetrahydro-13-oxodibenzo[b.g]bicyclo[3.3.1]nonane-6-carboxylate (***1a***)*

A 25 mL round-bottomed flask was charged with methyl propionylacetate (**2**) (65 mg, 64.0 mL, 0.50 mmol, 1 equiv), 4 mL of dry DMF and anhydrous potassium carbonate (138 mg, 1.00 mmol, 2 equiv). The mixture was stirred at 23 °C for 10 min and 2-fluoro-5-nitrobenzyl bromide (**3**) [12] (234 mg, 1.00 mmol, 2 equiv) was added. The suspension turned yellow and the reaction was stirred at 23 °C for 2 days. The crude reaction mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 25 mL), dried (Na_2SO_4) and concentrated under vacuum to give a light yellow oil. This oil was purified by PTLC eluted with 15% EtOAc in hexanes to give 140 mg (64%) of methyl 2,2-bis(2-fluoro-5-nitrobenzyl)-3-oxopentanoate (**5a**) as a light yellow solid, m.p. 112–114 °C. IR: 1741, 1716, 1532, 1345 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.17 (ddd, *J* = 9.0, 4.4, 2.8 Hz, 2H), 8.13 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 3.78 (s, 3H), 3.33 (apparent s, 4H), 2.44 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ 205.6, 171.2, 164.9 (d, *J* = 256.8 Hz), 144.1 (d, *J* = 2.8 Hz), 128.3 (d, *J* = 6.1 Hz), 125.1 (d, *J* = 10.4 Hz), 124.8 (d, *J* = 18.2 Hz), 116.3 (d, *J* = 25.8 Hz), 64.2, 52.8, 33.6, 32.6, 7.8; HRMS (*m*/*z*): Calcd for $C_{20}H_{18}F_2N_2O_7$: 436.1082, found: 436.1074.

To a solution of 140 mg (0.32 mmol) of **5a** in 4 mL of dry DMF was added anhydrous potassium carbonate (88 mg, 0.64 mmol) and the mixture was stirred at 75 °C for 1 h. At this time, TLC indicated that the reaction was complete. The crude reaction mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 25 mL), dried (Na_2SO_4) and concentrated under vacuum to give a tan solid. Purification by PTLC (25% EtOAc in hexanes) afforded 104 mg (82%) of **1a** as a light yellow solid, m.p. 267–268 °C; IR: 1739, 1732, 1530, 1351 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.16 (d, *J* = 2.7 Hz, 2H), 8.12 (dd, *J* = 8.8, 2.7 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 3.90 (ABd, *J* = 16.2 Hz, 2H), 3.77 (s, 3H), 3.52 (ABd, *J* = 16.2 Hz, 2H), 1.89 (s, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 206.3, 171.5, 147.9, 147.1, 136.1, 127.8, 124.1, 123.2, 54.8, 53.3, 53.0, 40.6, 18.2; HRMS (*m*/*z*): Calcd for $C_{20}H_{16}N_2O_7$: 396.0958, found: 396.0955. Anal. Calcd for $C_{20}H_{16}N_2O_7$: C, 60.61; H, 4.07; N, 7.07, found: C, 60.47; H, 4.11; N, 6.94.

Supplementary Materials: Copies of ^{1}H-NMR and ^{13}C-NMR spectra for the precursor and title compound, as well as six other derivatives are available online.

Author Contributions: Project conception, project administration, formal analysis and writing the manuscript text, R.A.B.; investigation, methodology, analysis and writing the experimental section, R.A.B. and D.R.N.; reviewing and editing, R.A.B. and D.R.N. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support for this work was obtained from the Oklahoma State University Foundation and the College of Arts and Sciences at Oklahoma State University. The authors are indebted to the OSU College of Arts and Sciences for funds to purchase several departmental instruments including an FT-IR and a 400 MHz NMR unit for the State-wide NMR facility. The NMR facility was initially established with support from the NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation and Conoco, Inc., Houston, TX, USA.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: D.R.N., an undergraduate researcher, acknowledges support from R.A.B.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Lednicer, D. *Strategies for Organic Drug Synthesis*, 2nd ed.; John Wiley and Sons, Inc.: New York, NY, USA, 2008; ISBN 978-0-470-19039-5.
2. Tietze, L. *Domino Reactions: Concepts for Efficient Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2014; ISBN 978-3-527-33432-2.
3. Nammalwar, B.; Bunce, R.A. Recent syntheses of 1,2,3,4-tetrahydroquinolines, 2,3-dihydro-4(1*H*)-quinolinones and 4(1*H*)-quinolinones using a domino strategy. *Molecules* **2014**, *19*, 204–232. [CrossRef] [PubMed]
4. Crowley, B.M.; Mori, Y.; McComas, C.C.; Tang, D.; Boger, D.L. Total synthesis of the ristocetin aglycon. *J. Am. Chem. Soc.* **2004**, *126*, 4310–4317. [CrossRef] [PubMed]
5. Miao, W.; Zhu, Z.; Li, Z.; Hao, E.; Jiao, L. Novel expanded porphyrinoids with multiple-inner-ring-fusion and/or tunable aromaticity. *Chin. Chem. Lett.* **2019**, *30*, 1895–1902. [CrossRef]
6. Chatterjee, T.; Srinivasan, A.; Ravikanth, M.; Chandrashekar, T.K. Smaragdyrins and sapphyrins analogues. *Chem. Rev.* **2017**, *117*, 3329–3376. [CrossRef] [PubMed]
7. Aoki, Y.; O'Brien, H.M.; Kawasaki, H.; Takaya, H.; Nakamura, M. Ligand-free iron-catalyzed C–F amination of diarylamines: A one pot regioselective synthesis of diaryl dihydrophenazines. *Org. Lett.* **2019**, *21*, 461–464. [CrossRef] [PubMed]
8. Masuda, Y.; Takeda, H.; Kuratsu, M.; Suzuki, S.; Kozaki, M.; Shiomi, D.; Sato, K.; Takui, T.; Okada, K. Radical-substituted dihydrophenazine radical cation salts: Molecular packing structure and bulk magnetic property. *Pure Appl. Chem.* **2010**, *82*, 1025–1032. [CrossRef]
9. Lee, J.; Shizu, K.; Tanaka, H.; Nakanotani, H.; Yasuda, T.; Kaji, H.; Adachi, C. Controlled emission colors and singlet-triplet energy gaps of dihydrophenazine-based thermally activated delayed fluorescence emitters. *J. Mater. Chem. C* **2015**, *3*, 2175–2181. [CrossRef]
10. Theriot, J.C.; Lim, C.-H.; Yang, H.; Ryan, M.D.; Musgrave, C.B.; Miyaki, G.M. Organocatalyzed atom transfer radical polymerization driven by visible light. *Science* **2016**, *352*, 1082–1086. [CrossRef] [PubMed]
11. Bunce, R.A.; Grant, M.T. 10-Alkyl-2,7-dinitro-9(10*H*)-acridinones by tandem S_NAr reactions. *Org. Prep. Proced. Int.* **2011**, *43*, 265–275. [CrossRef]
12. Bunce, R.A.; Rogers, D.; Nago, T.; Bryant, S.A. 4*H*-1-Benzopyrans by a tandem S_N2-S_NAr reaction. *J. Heterocycl. Chem.* **2008**, *45*, 547–550. [CrossRef]