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Design and synthesis of novel benzopyrazolodiazepinones via intra-molecular alkylation of α-alkylcarbonyl radicals mediated by dilauroylperoxide

Luz M. Jaramillo-Gómez, Gerson López, Braulio Insuasty, Jairo Quiroga, Rodrigo Abonia *

Department of Chemistry, Universidad del Valle, A.A. 25360 Cali, Colombia

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ABSTRACT

Using a tin-free strategy, novel 4*H*-benzo[*f*]pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-ones were synthesized in acceptable yields via intra-molecular alkylation over a benzene ring, of α-alkylcarbonyl radicals generated from ethyl pyrazolylbenzylaminoxanthates, using dilauroyl peroxide (DLP) as the radical initiator.

Fused-tricyclic benzazepine and benzodiazepine moieties are important frameworks owing to their presence in naturally occurring as well as in synthetic products of pharmaceutical interest.[1] Thus Cephalotaxine **1** is reported as the major alkaloid found in the evergreen plum yews Cephalotaxus, which is indigenous in South-East Asia. This alkaloid by itself shows no pronounced biological activity, but its succinate, known as Deoxyharringtonine **2**, has displayed the highest IC_{50} value against leukemic cells,[1d–g] compounds **3** were obtained to be screened as novel and selective peripheral-type benzodiazepine receptor (PBR) ligands and to evaluate their ability to modulate steroid biosynthesis in rats,[1h] diazepine **4** belongs to a family of potential antitumor agents obtained from a naturally occurring *Streptomyces* species and recently by synthetic approaches[1i] while diazepines **5** were designed and synthesized as novel and potent arginine vasopressin antagonists[1j] (Fig. 1).

Xanthates have recently emerged as versatile intermediates in the formation of novel and diverse organic systems via free-radical reactions.[2] Particularly, several spiro-compounds have recently been synthesized via intra-molecular alkylation of alkyl-radical species generated from their corresponding xanthate derivatives involving DLP (dilauroyl peroxide) as the radical initiator.[2c]

In continuation of our current studies on the use of diverse strategies toward the formation of new C–C bonds via free-radical intermediates[3] and the synthesis and chemical transformation of benzylaminopyrazoles,[4] we describe herein a straightforward and three-step protocol, involving a free-radical pathway, for the synthesis of the novel 4*H*-benzo[*f*]pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-ones **9**, Scheme 1. These compounds are closely related to those biologically active structures shown in Figure 1, for sharing a similar ABC core.

For this purpose a series of new chloroacetyl derivatives **7** was initially obtained by treatment of the corresponding aminopyraz-

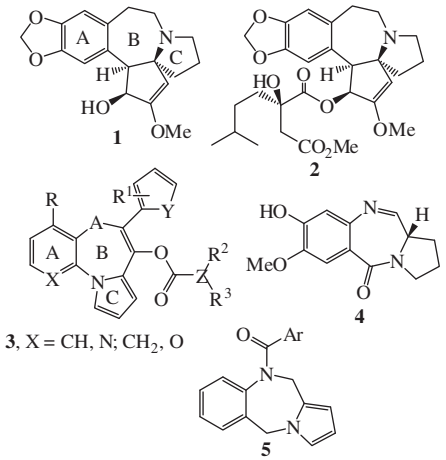

Figure 1. Some fused-polycyclic azepine derivatives of biological interest.

* Corresponding author. Tel./fax: +57 2 3393248.
E-mail address: rodrigo.abonia@correounivalle.edu.co (R. Abonia).

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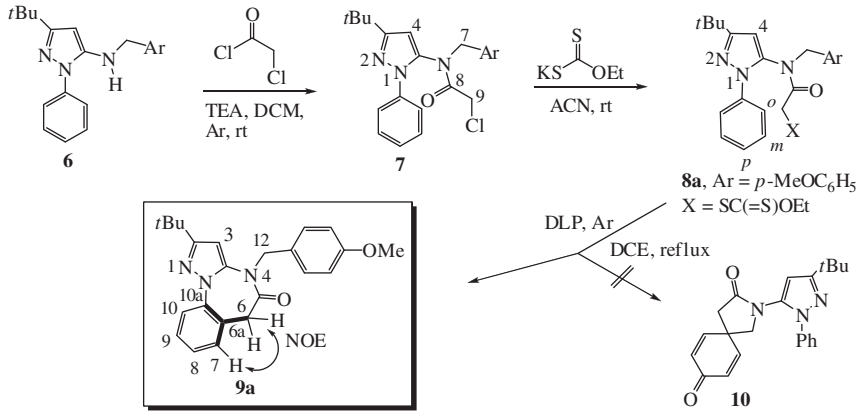

Scheme 1. Three step synthesis of novel benzopyrazolodiazepinones **9** promoted by DLP.

oles **6** with chloroacetyl chloride in DCM/TEA as shown in Scheme 1.

Compounds **7** were obtained in 56–91% yield after stirring the reaction mixtures over argon atmosphere at room temperature and purification of the crudes by column chromatography on silica gel.[5] Table 1 summarizes the obtained results.

Compounds **7** were completely characterized by analytical and spectroscopic methods (see Supplementary data). The most relevant signal in the FTIR spectra corresponded to an intense absorption band at 1671–1692 cm^{-1}, which was assigned to the carbonyl group of the amide functionality. The most relevant feature in the ^1H NMR spectra corresponded to the unequivalence of the four geminal methylene protons. Therefore, four sets of doublets (δ = 3.75–3.91 ppm, δ = 3.92–3.95 ppm, δ = 3.96–4.13 ppm and δ = 5.14–5.30 ppm, respectively, 1H each one) were observed. In the ^{13}C NMR spectra a signal at (δ = 40.5–41.9 ppm) assigned to the new methylene group of the chloroacetyl fragment is the most relevant feature. Finally, the growing of single-crystals of compound **7a** from a solution in ethanol and investigation by X-ray diffraction unambiguously confirmed the assigned structures for compounds **7**.[6]

Treatment of chloroacetyl derivatives **7** with potassium O-ethylcarbonodithioate in ACN at room temperature afforded the expected xanthates **8** in 75–94% yield, Scheme 1, Table 1. In consequence compounds **8** were formed from a nucleophilic substitution of the chlorine atom in **7** by the potassium xanthate salt.[7]

The structure of compounds **8** was also assigned by analytical and spectroscopic methods (see Supplementary data). The most relevant features in the ^1H NMR spectra corresponded to a triplet (δ = 1.31–1.37 ppm, 3H) and a quartet (δ = 4.55–4.58 ppm, 2H) assigned to the methyl and methylene groups, respectively, of the xanthate functionality. Like compounds **7** the unequivalence of the same four geminal methylene protons was observed in **8** as doublets at (δ = 3.53–3.63 ppm, δ = 3.89–4.05 ppm, δ = 3.98–4.13 ppm and δ = 5.26–5.40 ppm, respectively). Growing of single-crystals of compounds **8b** and **8d** from solutions in ethanol and investigation by X-ray diffraction unambiguously confirmed the assigned structures for compounds **8**.[6]

It is worth mentioning that the subsequent cyclization process of compounds **8** was initially planned with the expectation to obtain new examples of spiro-derivatives **10** as shown in Scheme 1. In this sense, following a similar procedure like described by Miranda and co-workers,[2c] compound **8a** (1 mmol) was treated with DLP portion-wise (1.8 mmol) in DCE at reflux for 8 h. The reaction was monitored by TLC and after total consumption of the starting material **8a**, several compounds were formed and the main component was isolated and purified by column chromatography on silica gel using DCM as eluent.[8] The ^1H NMR spectrum of this product showed the following main signals. A singlet (δ = 3.69 ppm, 2H) assigned to a methylene group and a singlet (δ = 3.77 ppm, 3H) corresponding to a methoxy group. It was also observed as a singlet (δ = 4.86 ppm, 2H) corresponding to a second methylene group and a singlet (δ = 5.92 ppm, 1H) assigned to the 4-H proton of the pyrazolic moiety. Two doublets at (δ = 6.79 ppm, J = 8.0 Hz, 2H and 7.05 ppm, J = 8.0 Hz, 2H, respectively) showed that the *p*-methoxybenzyl fragment was unchanged during the course of reaction. Finally a triplet at (δ = 7.31 ppm, J = 8.0 Hz, 1H), a doublet at (δ = 7.35 ppm, J = 8.0 Hz, 1H), a triplet at (δ = 7.43 ppm, J = 8.0 Hz, 1H) and a doublet at (δ = 7.75 ppm, J = 8.0 Hz, 1H) indicated that one of the five Ph-protons proceeding from the starting xanthate **8a** is absent in the structure of this new isolated product. According to Scheme 1, the structure which matched with all ^1H NMR signals corresponded to compound **9a** but not the spiro-compound **10**. Moreover ^{13}C NMR showed the expected 19 different carbon atoms (eight of them were Cq) and the DEPT experiment showed two methylenes and seven aromatic CH signals, in agreement with structure **9a**. A molecular ion in the mass spectrum (m/z = 375, 26%) and a base peak (m/z = 121, 100% corresponding to the methoxytropylium ion) were also in agreement with the proposed structure **9a**.

Once confirmed the structure of compound **9a** the calculated yield corresponded to 52% yield. To evaluate the generality of this approach, the reaction condition described in the last step of Scheme 1 was extended to other xanthate derivatives **8b–i** finding a similar behavior and the same synthetic orientation in all cases. In Table 1 and (Supplementary data) it is summarized the obtained results.

Although attempts to grow single single-crystals for X-ray diffraction of compounds **9** were unfruitful, all proton and carbon atoms of the benzopyrazolodiazepine frameworks were fully assigned from ^1H, ^{13}C NMR. Particularly, 2D-NMR (HSQC, HMBC and NOESY) experiments confirmed that the cyclization process involved the phenyl C-*ortho* of the xanthates **8** and no other carbon atom. In this sense, the 6-CH_2 hydrogens appearing as a singlet at 3.68–3.73 ppm showed HMBC correlations with C-6a, C-7, and C-10a carbon atoms, appearing, respectively, at 126.4–129.1, 128.9–130.8, and 137.1–139.7 ppm. Additionally, NOESY correlations of the same 6-CH_2 protons with the 7-CH protons confirmed the spatial proximity of such protons and hence the connectivity of the 6-C and 6a-C carbon atoms supporting unambiguously the formation of the structures **9** as depicted in Scheme 1.

In summary, the straightforward synthesis of new 1,3-benzopyrazolodiazepinones **9** was performed starting from ethyl pyrazolylbenzylaminoxanthates. This tin-free strategy involved an unusual and selective α-alkylcarbonyl radical cyclization process

Table 1
Analytical data for compounds (**7**, **8** and **9**)**a–i**

Entry	Ar	Compound **7**		Compound **8**		Compound **9**	
		Mp (°C)	Yield %	Mp (°C)	Yield %	Mp (°C)	Yield %
a	*p*-$CH_3OC_6H_4$	80–81	86	110–111	93	153–154	52
b	*p*-$CH_3C_6H_4$	115–116	73	86–87	94	181–182	58
c	3,4,5-$(CH_3O)_3C_6H_2$	129–130	80	98–99	90	130–131	52
d	*p*-ClC_6H_4	159–160	82	94–95	92	193–194	54
e	*p*-$NO_2C_6H_4$	172–173	56	118–119	85	197–198	60
f	*p*-BrC_6H_4	149–150	82	95–96	80	157–158	54
g	4-OH-3-$CH_3OC_6H_3$	134–136	80	106–108	84	151–153	48
h	*p*-$(CH_3)_2NC_6H_4$	104–105	63	131–132	75	140–141	50
i	3,4-$(CH_3O)_2C_6H_3$	76–77	91	134–135	94	179–180	56

over the 1-phenyl ring of the 5-aminopyrazole derivatives **6** promoted by dilauroyl peroxide (DLP) as the radical initiator. This radical-mediated approach resulted in a useful synthetic alternative because this particular type of benzodiazepinones has not been obtained previously under ionic reaction conditions. Studies directed to improve the efficiency of the last step in Scheme 1, the exploration of the broadest of this strategy and to evaluate the practical usefulness of the obtained products **9** are currently in progress.

Acknowledgments

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5. *General procedure for the synthesis of chloroacetyl derivatives* **7**. A mixture of chloroacetyl chloride (0.1 mL, 1.25 mmol), dichloromethane (8 mL) and triethylamine (0.3 mL, 2.15 mmol) was cooled on an ice-water bath under argon atmosphere. Then the corresponding arylpyrazolylamine **6** (0.6 mmol), dissolved in dichloromethane (2 mL) was added and the solution was removed from the cold bath. Then the mixture was stirred at room temperature for 10–24 h and after complete disappearance of the starting material **6** (TLC control), the solvent was evaporated under reduced pressure and the residues were purified by column chromatography on silica gel (AcOEt/DCM gradient) to obtain compounds **7**. All reactions started with 200 mg of compound **6**. *N*-(3-*tert*-Butyl-1-phenyl-1*H*-pyrazol-5-yl)-2-chloro-*N*-(4-methoxy-benzyl)acetamide **7a**. Isolated as yellow solid, yield: 212 mg, IR (KBr disk, cm^{-1}) 1685 (C=O), 1251 (C–O), 1032 (C–O); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.45–7.38 (m, 4H, Ar-H), 7.34 (t, *J* = 8.0, 1H, Ar-H), 7.08 (d, *J* = 8.0, 2H, Ar-H), 6.79 (d, *J* = 8.0, 2H, Ar-H), 5.85 (s, 1H, 4-H), 5.26 (d, *J* = 12.0, 1H, 7b-H), 3.99–3.92 (m, 2H, 9b-H and 7a-H), 3.79 (br s, 4H, 9a-H and OCH_3), 1.30 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.5 (C=O), 162.4 (Cq), 159.5 (Cq), 138.4 (Cq), 137.7 (Cq), 130.6, 129.6, 127.7, 127.6 (Cq), 122.8, 113.8, 103.3 (C-4), 55.2 (OCH_3), 52.0 (C-7), 41.8 (C-9), 32.5 (Cq, *t*Bu), 30.1 (CH_3, *t*Bu). *m*/*z* (ESI, %) 413/411 (10/30, $M^{+\cdot}$), 226 (43), 121 (100, C_8H_9O), 77 (7, Ph). Anal. Calcd for $C_{23}H_{26}ClN_3O_2$: C, 67.06; H, 6.36; N, 10.20. Found: C, 67.32; H, 6.36; N, 9.82.
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7. *General procedure for the synthesis of xanthates* **8**. A mixture of the corresponding chloroacetyl derivative **7** (0.5 mmol) and potassium *O*-ethyl carbonodithioate (0.75 mmol) was dissolved in acetonitrile (6–8 mL) and kept in the absence of light. The mixture was stirred at room temperature for 2–3 h and after complete disappearance of the starting material **7** (TLC control), the solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (AcOEt/DCM gradient) yielding compounds **8**. All reactions started with 200 mg of compound **7**. *S*-2-[(3-*tert*-Butyl-1-phenyl-1*H*-pyrazol-5-yl)(4-methoxybenzyl)amino]-2-oxoethyl-*O*-ethylcarbonodithioate **8a**. Isolated as yellow solid, yield: 225 mg. IR (KBr disk, cm^{-1}) 1691 (C=O), 1237 (C–O), 1032 br (C–O); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.44–7.34 (m, 5H, Ar-H), 7.12 (d, *J* = 8.0, 2H, Ar-H), 6.81 (d, *J* = 8.0, 2H, Ar-H), 5.88 (s, 1H, 4-H), 5.32 (d, *J* = 12.0, 1H, 7b-H), 4.59 (q, *J* = 8.0, 2H, OCH_2), 4.01 (d, *J* = 12.0, 1H, 7a-H), 3.92 (d, *J* = 16.0, 1H, 9b-H), 3.80 (s, 3H, OCH_3), 3.55 (d, *J* = 16.0, 1H, 9a-H), 1.36 (t, *J* = 8.0, 3H, CH_3), 1.31 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 213.1 (C=S), 167.0 (C=O), 162.4 (Cq), 159.4 (Cq), 138.6 (Cq), 138.4 (Cq), 130.7, 129.5, 128.0 (Cq), 127.5, 122.9, 113.8, 103.3 (C-4), 70.5 (OCH_2), 52.0 (C-7), 39.4 (C-9), 32.5 (Cq, *t*Bu), 30.1 (CH_3, *t*Bu), 13.7 (CH_3). *m*/*z* (ESI, %) 497 (2, $M^{+\cdot}$), 376 (36), 344 (56), 121 (100, C_8H_9O), 77 (18), 29 (13). Anal. Calcd for $C_{26}H_{31}N_3O_3S_2$: C, 62.75; H, 6.28; N, 8.44. Found: C, 62.88; H, 6.37; N, 8.60.
8. *General procedure for the synthesis of the pyrazolodiazepinones* **9**. A mixture of the corresponding xanthate **8** (1.0 mmol) and anhyd DCE (6–8 mL) was heated to reflux under argon atmosphere. Then DLP (1.8 mmol) was added portion-wise during 6–8 h and after complete disappearance of the starting material **8** (TLC control), the solvent was removed under reduced pressure and the main component of the residue was isolated and purified by column chromatography on silica gel (AcOEt/DCM gradient) yielding compounds **9**. All reactions started with 200 mg of compound **8**. 2-*tert*-Butyl-4-(4-methoxybenzyl)-4*H*-benzo[*f*]pyrazolo[1,5-*a*][1,3]diazepin-5(6*H*)-one **9a**. Isolated as yellow solid, yield: 79 mg. IR (KBr disk, cm^{-1}) 1670 (C=O), 1240 (C–O), 1038, (C–O); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, *J* = 8.0, 1H, 10-H), 7.43 (t, *J* = 8.0, 1H, 9-H), 7.35 (d, *J* = 8.0, 1H, 7-H), 7.31 (t, *J* = 8.0, 1H, 8-H), 7.05 (d, *J* = 8.0, 2H, Ar-H), 6.79 (d, *J* = 8.0, 2H, Ar-H), 5.92 (s, 1H, 3-H), 4.86 (br s, 2H, 12-H), 3.77 (s, 3H, OCH_3), 3.69 (s, 2H, 6-H), 1.31 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.1 (C=O), 162.8 (Cq), 158.9 (Cq), 141.3 (Cq), 137.4 (Cq), 128.9 (C-7), 128.8 (Cq and C-9), 128.5, 127.6 (C-8), 126.8 (Cq), 122.7 (C-10), 114.0, 94.7 (C-3), 55.2 (OCH_3), 51.8 (C-12), 41.0 (C-6), 32.5 (Cq, *t*Bu), 30.2 (CH_3, *t*Bu). *m*/*z* (ESI, %) 375 (26, $M^{+\cdot}$), 151 (36), 121 (100, C_8H_9O), 120.0 (100), 91 (62), 77 (88), 57 (53). Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.69; H, 6.48; N, 11.25.