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Benzaldehyde-derived chloroformates and their application towards the synthesis of methoxyfenozide-*N*-[(acyloxy)benzyloxy]carbonyl derivatives

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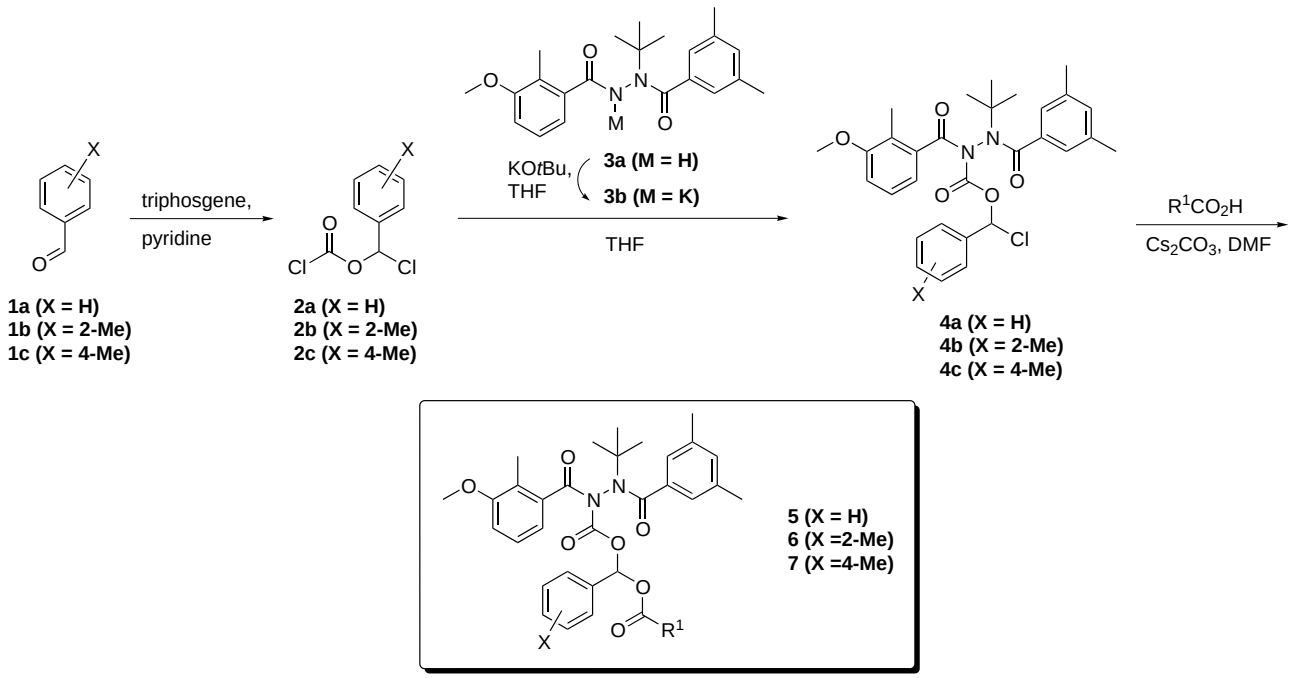
Abstract—The synthesis of a series of substituted benzaldehyde-derived chloroformates and their application towards the synthesis of a diverse series of novel insecticidally active carboxylic acid [*N′-tert*-butyl-*N′*-(3,5-dimethylbenzoyl)-*N*-(3-methoxy-2-methylbenzoyl)hydrazinocarbonyloxy]phenylmethyl esters, prepared in a parallel synthesis fashion, is reported.

N-tert-Butyl diacyl hydrazines are an important class of environmentally safe, selective insecticidal compounds.[1] One such example, methoxyfenozide (**3a**),[2] is commercially used as an ecdysone agonist to selectively control *Lepidopterous* larvae on cotton, vegetables, apples, and pome fruit (Scheme 1).[3] Methoxyfenozide, due to its highly crystalline nature and low water solubility (3.0 ppm), tends to have a non-optimal use



Scheme 1.

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rate and formulation difficulties.[3] As described in a previous publication,[4] our group has incorporated [(acyloxy)alkoxy]carbonyl and (acyloxy)alkyl moieties into diacyl hydrazines which has resulted in drastic changes in the physical properties associated with this insecticidal class of compounds while simultaneously increasing biological efficacy. The use of chloroalkyl chloroformates in the synthesis of *N*-[(acyloxy)-alkoxy]carbonyl derivatives is quite prevalent in the literature.[5,6] However, chlorobenzyl chloroformates, despite reports to their synthesis,[7] have not received the same attention in the synthesis of *N*-[(acyloxy)-benzyloxy]carbonyl derivatives. One reason could be the use of undesirable reagents such as phosgene gas or solvents such as carbon tetrachloride in their syntheses. In this paper, we will describe the synthesis of benzaldehyde-derived chloroformates via treatment of substituted benzaldehydes with triphosgene in diethyl ether and the application of these chloroformates to the synthesis of various methoxyfenozide-*N*-[(acyloxy)-benzyloxy]carbonyl derivatives (**5**–**7**, Scheme 1).

We began our efforts by first assembling the benzaldehyde-derived chloroformates **2a**–**c**. Chloroformate **2a** (X = H) was smoothly synthesized following the procedures of Coghlan and Caley in which benzaldehyde **1a** (X = H) was treated with triphosgene in the presence of a catalytic amount of pyridine in carbon tetrachloride.[7] However, with the restrictions associated with carbon tetrachloride, we were compelled to explore alternate solvent systems. Diethyl ether proved to be a viable solvent system for the synthesis of chloroformates **2b**,**c**.[8] However, due to their instability,[8] chloroformates **2a**–**c** were synthesized and then directly allowed to react with the potassium salt of methoxyfenozide (**3b**) to afford stable, isolable compounds **4a**–**c**, which were fully characterized.[9] Intermediates **4a**–**c** were treated with various carboxylic acids (R^1CO_2H) in the presence of cesium carbonate in DMF in a parallel synthesis fashion to afford various methoxyfenozide-*N*-[(acyloxy)-benzyloxy]carbonyl derivatives (**5**–**7**) (Scheme 1, Table 1).[10]

In conclusion, various substituted benzaldehyde-derived chloroformates (**2**) were synthesized through the reaction of substituted benzaldehydes with triphosgene in the presence of pyridine in diethyl ether. The chloroformates proved to be thermally unstable but were reacted first with the potassium salt of methoxyfenozide (**3b**) to

Table 1. Compounds **5**–**7** prepared via parallel synthesis[11] and analyzed by LC/UV/MS[12]

Compound no.	X	R^1	Mass found	% Purity by UV
5a	H	1-Methyl-1*H*-pyrrol-2-yl	625	96
5b	H	Cyclopropyl	586	93
5c	H	2-(2-Thienyl)ethenyl	654	94
5d	H	2-Hexyl	630	100
5e	H	3-Thienyl	628	100
5f	H	3-Pyridyl	623	100
5g	H	Methyl	560	100
5h	H	Phenyl	622	96
5i	H	2-Pyridyl	623	92
5j	H	3-Hydroxy-4-methoxyphenyl	668	89
5k	H	Tetrahydrofur-3-yl	616	100
5l	H	$C(CH_3)_3$	602	97
6a	2-Me	Methyl	574	95
6b	2-Me	Ethenyl	586	94
6c	2-Me	Phenyl	636	100
6d	2-Me	2-(2-Thienyl)ethenyl	668	92
6e	2-Me	2-Methylcyclopropyl	614	100
6f	2-Me	Phenoxymethyl	666	95
6g	2-Me	2-Pyridyl	637	100
6h	2-Me	Cyclopropyl	600	100
7a	4-Me	Methyl	574	95
7b	4-Me	Tetrahydrofur-2-yl	630	91
7c	4-Me	Ethyl	588	100
7d	4-Me	Phenyl	636	100
7e	4-Me	2-Pyridyl	637	100
7f	4-Me	1-(*tert*-Butoxycarbonylamino)propyl	717	100
7g	4-Me	Methoxymethyl	604	92
7h	4-Me	3-(2-Thienyl)propyl	684	95
7i	4-Me	2-(2-Thienyl)ethenyl	668	100
7j	4-Me	2-Hexyl	644	100
7k	4-Me	Tetrahydrofur-3-yl	630	100
7l	4-Me	2-(2-Fluorophenyl)ethenyl	680	100
7m	4-Me	3-Methyl-2-thienyl	656	93

afford stable, isolable intermediates **4a–c** which then were reacted with various carboxylic acids to afford novel methoxyfenozide-*N*-[(acyloxy)benzyloxy]carbonyl derivatives **5–7**.

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References

1. Thomson, W. T. *Agricultural Chemicals*, *Book* 1, *Insecticides*, 14th ed.; Thomson Publications: Fresno, CA, 1998; pp. 142–144.
2. Lidert, Z.; Le, D. P.; Hormann, R. E.; Opie, T. R. US 5530028, *Chem. Abstr.* 1996, 125, 161132.
3. Tomlin, C. D. S. *The Pesticide Manual*, 11th ed.; British Crop Protection Council: Farnham, Surrey GU9 7PH, UK, 1997; pp. 388–389.
4. Mulvihill, M. J.; MacDougall, B. S.; Ajello, C.; Martinez-Teipel, B.; Joseph, R.; Weaver, D. G.; Nguyen, D. V.; Gusev, A.; Weirenga, J. M.; Mathis, W. D. *Synthesis* **2001**, submitted for publication.
5. Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, CA, 1992; pp. 361–363.
6. Folkmann, M.; Lund, F. J. *Synthesis* **1990**, 1159–1166.
7. Coghlan, M. J.; Caley, B. A. *Tetrahedron Lett.* **1989**, *30*, 2033–2036 and references cited therein.
8. Compounds **2a–c**: Chloroformate **2a** was synthesized via the carbon tetrachloride route while chloroformates **2b**,**c** were synthesized via the diethyl ether route. All chloroformates **2a–c** were directly carried on to the next reaction (due to thermal stability issues) with the potassium salt of methoxyfenozide to afford stable, isolable compounds **4a–c** which were fully characterized as described below in Ref. 9.
9. Compounds **4a–c**: Compound **4a**: mp = 103–105°C; IR ν (cm^{-1}): 1766, 1712, 1676; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.62 (s, 9H), 1.95 (bs, 3H), 2.20 (s, 6H), 3.77 (s, 3H), 6.70–7.30 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 14.5, 23.3, 29.8, 57.6, 65.1, 88.0, 113.7, 118.9, 125.0, 126.5, 128.3, 130.7, 132.4, 133.0, 137.8, 138.5, 139.4, 140.3, 153.7, 159.9, 171.6, 174.9; Anal. calcd for $C_{30}H_{33}ClN_2O_5$: C, 67.09; H, 6.19; N, 5.22. Found: C, 66.88; H, 6.09; N, 5.15. Compound **4b**: mp = 111–113°C; IR ν (cm^{-1}): 2949, 1765, 1712, 1677; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.61 (s, 9H), 1.95 (bs, 3H), 2.16 (bs, 6H), 2.24 (s, 3H), 3.72 (s, 3H), 6.62–7.27 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.4, 18.6, 21.0, 27.6, 55.3, 62.9, 83.5, 111.5, 116.8, 122.8, 124.2, 126.1, 126.2, 126.3, 129.9, 130.6, 130.7, 133.6, 134.4, 136.2, 137.2, 138.1, 151.7, 157.6, 169.3, 172.6; Anal. calcd for $C_{31}H_{35}ClN_2O_5$: C, 67.57; H, 6.40; N, 5.08. Found: C, 67.69; H, 6.15; N, 5.05. Compound **4c**: mp = 123–125°C; IR ν (cm^{-1}): 1766, 1713, 1676; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.58 (s, 9H), 1.95 (bs, 3H), 2.18 (s, 6H), 2.34 (s, 3H), 3.74 (s, 3H), 6.70–7.10 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.2, 21.9, 22.2, 28.5, 56.3, 63.8, 86.8, 112.4, 117.6, 123.7, 125.2, 126.9, 130.0, 131.7, 133.7, 137.3, 138.1, 139.0, 141.2, 152.4, 158.6, 170.3, 173.5; Anal. calcd for $C_{31}H_{35}ClN_2O_5$: C, 67.57; H, 6.40; N, 5.08. Found: C, 67.65; H, 6.11; N, 5.36.
10. A typical reaction sequence in the synthesis of chloroformates **2a–c**, compounds **4a–c**, and compounds **5–7** is represented by **2b**, **4b**, and **6a**: Synthesis of compound **2b**: A 1000 mL diethyl ether solution of 2-methylbenzaldehyde (75.0 g, 620.0 mmol), cooled to −20°C, was charged with triphosgene (205.0 g, 690.0 mmol) followed by pyridine (6.0 mL, 62.0 mmol). The reaction was allowed to warm to room temperature (rt) and stir for 2 h, after which time the reaction mixture was filtered through Celite®. The filtrate was concentrated in vacuo to afford 103 g of chloroformate **2b** in 75% yield (95% purity by ^1H and ^{13}C NMR). Chloroformate **2b** (1.36 g, 6.20 mmol) then was added in one portion to a 0°C THF solution of the potassium salt of methoxyfenozide (**3b**), prepared by treating methoxyfenozide **3a** (1.92 g, 5.20 mmol) with potassium *tert*-butoxide (0.58 g, 5.20 mmol) in 50 mL of THF at rt. The reaction was allowed to warm to rt and stir for 4 h, after which time the solvent was removed in vacuo and the crude mixture subjected to silica gel column chromatography (90:10 hexanes/EtOAc) to afford 2.0 g (70%) of the desired compound **4b**. Preparation of compounds **5–7** via parallel synthesis: Synthesis of compound **6a**: Cs_2CO_3 (70 mg, 0.22 mmol) in 500 μL DMF was delivered to a 96 well reaction block (496 MBS, Advanced Chemtech) followed by acetic acid (13 mg, 0.22 mmol). The block was stirred at rt for 30 min, at which time a solution of **4b** (100 mg, 0.18 mmol in 500 μL DMF) was delivered. Stirring was continued at rt for up to 48 h. The reaction was filtered into the cleavage block, the solvent was removed in a Genevac HT-12 and the residue was taken up in CH_2Cl_2 and chromatographed on a preconditioned (hexanes) 2 g silica solid phase extraction cartridge (gradient of hexanes to 1:1 hexanes/EtOAc) yielding 65 mg (65%) of compound **6a** as a white solid; mp = 70–72°C; IR ν (cm^{-1}): 2945, 1767, 1711, 1675; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.64 (s, 9H), 1.95 (bs, 3H), 2.05 (s, 3H), 2.08 (s, 6H), 2.35 (s, 3H), 3.74 (s, 3H), 6.68–7.32 (m, 10H), 7.64 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.7, 18.9, 20.7, 21.0, 27.5, 55.4, 62.7, 91.0, 111.2, 116.7, 122.7, 124.1, 125.8, 126.2, 127.5, 130.2, 130.6, 131.0, 131.9, 136.3, 136.7, 137.3, 138.0, 151.3, 157.5, 168.3, 169.6, 172.6; Anal. calcd for $C_{33}H_{38}N_2O_7$: C, 68.97; H, 6.67; N, 4.87. Found: C, 69.08; H, 6.72; N, 4.90.
11. Compound **6a** was fully characterized as a representative example of this class of chemistry as described in Ref. 10. Compounds **5a–l**, **6b–h**, and **7a–m** were prepared via parallel synthesis and analyzed by LC/UV/MS as presented in Table 1.
12. For liquid chromatography (LC)/ultraviolet (UV) mass spectrometry (MS) analysis, the samples were dissolved in CH_3CN:H_2O (1:1) at concentrations of 100 μg/mL to 1000 μg/mL. The LC/UV/MS analysis was performed using the HPLC 1100-VG Platform. The UV and MS instruments were connected in sequence, and the analysis was carried out in one injection where LC/UV afforded the purity (%) and MS confirmed the molecular weight.

UV analysis was carried out using a scanning diode array detector (200–300 nm). MS analysis was carried out in positive scanning mode (100–1000 daltons). A short C18 HPLC column (3 mm ID, 5 cm length) was used with a flow rate of 1 mL/min. The eluent was split 1:25 after UV detection and 1 part was sent to the MS. The typical HPLC gradient was 25:75 H_2O:CH_3CN to 100% acetonitrile over 5 min (0.1% formic acid added). Injection volume varied between 1 and 25 μL. In some cases, it was necessary to change certain parameters, e.g. ion mode (positive or negative), UV wavelength, or solvent buffer (no buffer, formic acid, acetic acid, or ammonia acetate). The data is presented in Table 1.