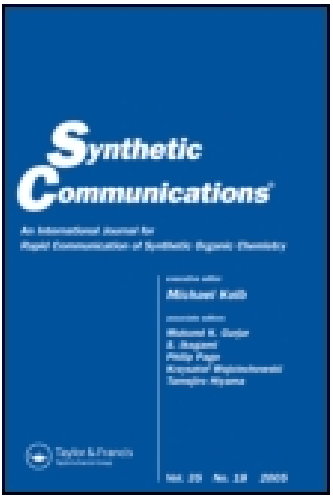

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Microwave-Assisted One-Step Synthesis of Substituted 2-Chloromethyl-1,3,4-oxadiazoles

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ABSTRACT

We have developed a simple one-step synthesis of 2-chloromethyl-1,3,4-oxadiazoles from commercially available acylhydrazides using 1-chloro-2,2,2-trimethoxyethane as a solvent under microwave irradiation.

INTRODUCTION

Numerous compounds containing 1,3,4-oxadiazoles have been evaluated for their antibacterial, fungicidal, and insecticidal activity.[1–3] Furthermore, 1,3,4-oxadiazoles have been used as peptide mimetics due to their particular geometric and electrostatic properties,[4] exemplified by the nonpeptidic

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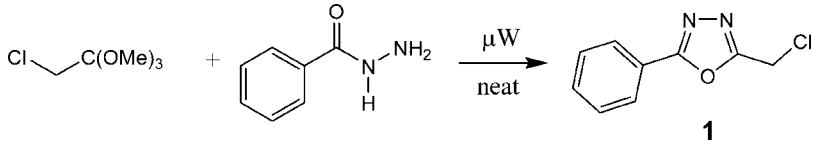
inhibitors of human neutrophil elastase that also have favorable pharmacokinetic and safety profiles.[5] Many of these compounds can be prepared by a simple alkylation using the corresponding 2-chloromethyl-1,3,4-oxadiazoles.[1,3,6] Synthetic approaches to obtaining these electrophilic building blocks include multi-step procedures that require a conventional aqueous workup.[7–10]

We were interested in developing a synthesis of 2-chloromethyl-l,3,4-oxadiazoles that could simplify the parallel production of these peptide mimetic building blocks. The desired synthesis should be carried out in one-step from inexpensive commercially available starting materials, and could be further simplified by the exclusion of an aqueous workup prior to purification. Herein, we report that benzoic hydrazide readily converts into 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (**1**) using 1-chloro-2,2,2-trimethoxyethane as a solvent under microwave irradiation (μW, Sch. 1), and that this reaction is then directly purified by chromatography. After optimization of this reaction, we explored the effect of substituted phenyl acyl hydrazides on this one-step synthesis.

During the optimization of this reaction (μW, Sch. 1), we kept the time constant at 300 sec while increasing the temperature in 20°C increments, and observed that microwave irradiation at a temperature of 160°C gave the highest yield of 68% (Table 1, compare entries 1–8). Doubling and tripling the reaction time to 600 and 900 sec while maintaining the temperature at 160°C, did not affect the yield significantly (Table 1, entries 9 and 10), and lead to the formation of by-products. In addition, we sought to improve the yield of this reaction by removal of methanol with the use of a known adsorbent such as molecular sieves of the relevant pore size.[11] However, the addition of 5 Å molecular sieves while keeping the temperature at 160°C for 300 sec, only increased the yield by 5% (Table 1, entry 11).

We then applied automated microwave irradiation to many substituted phenyl hydrazides using the conditions found in Table 1, entry 6. During this parallel synthesis, we observed that different substituents affected the yield for the formation of chloromethyl-l,3,4-oxadiazoles (Table 2, entries 2–15).



Scheme 1.

Table 1. Optimization of the reaction of benzoic hydrazide with 1-chloro-2,2,2-trimethoxyethane.

Entry	Temperature (°C)	Time of μW, irradiation (sec)	Yield (%)
1	60	300	0[a]
2	80	300	27[a]
3	100	300	47[a], 47[b]
4	120	300	56[a]
5	140	300	67[a]
6	160	300	68[a]
7	180	300	59[a]
8	200	300	47[a]
9	160	600	71[a]
10	160	900	74[a]
11	160	300	73[a,c]

[a]Yield determined by HPLC analysis with external standard calibration curve at 254 nm.
[b]Isolated yield.
[c]5 Å molecular sieves.

The methoxy, fluoro, and chloro substituents were fully explored (*o*, *m*, and *p*, Table 2, entries 2–10) demonstrating a trend of markedly lower yields for the 2-substitution (Table 2, entries 4, 7, and 10) as compared to their 4- and 3-substituted counterparts (Table 2, entries 2, 3, 5, 6, 8, and 9). This trend is not consistent with a pronounced electronic effect, but rather with steric bulk, and is further supported by the lower yield observed for 2-trifluoromethyl substituted oxadiazole (Table 2, entry 11). Although all substitution patterns afforded useful yields, the 4-substituted phenyl derivatives were further explored (Table 2, entries 12–15). These 4-substituted derivatives are favorable from a medicinal chemistry perspective, because hydrogen replacements at this position remove a known site of metabolism (e.g. phase I hydroxylation), and therefore can enhance oral bioavailability. We observed that a few substituted oxadiazoles with lipophilic groups, crystallized upon cooling allowing for a simple isolation by filtration (Table 2, entries 14 and 15).

In conclusion, we have developed a rapid and simple one-step method for the preparation of substituted 2-chloromethyl-1,3,4-oxadiazoles from the corresponding commercially available acyl hydrazides. The short reaction times, availability of reagents, and absence of aqueous workup provide an attractive protocol for rapidly generating these building blocks.

Table 2. Chemical yields and analytical data for compounds 1–15.

No.	R	Isolation	Yield (%)	Purity[a]	ESI^+ MS found	^{1}HNMR: (δ, 400 MHz, $CDCl_3$)
1	Ph	HPLC[b]	55	99.65	195.0	8.07 (dd, $J = 8.2$, 1.6 Hz, 2H), 7.53 (m, 3H), 4.78 (s, 2H)
2	4-MeO–C_6H_4	HPLC[b]	93	98.56	225.0	8.00 (d, $J = 7.0$ Hz, 2H), 7.00 (d, $J = 9.0$ Hz, 2H), 4.75 (s, 1H), 3.87 (s, 3H)
3	3-MeO–C_6H_4	Flash	61	97.07	225.0	7.64 (d, $J = 7.43$ Hz, 1H), 7.60 (d, $J = 2.35$ Hz, 1H), 7.42 (m, 1H), 7.10 (dd, $J = 7.83$, 3.13 Hz, 1H), 3.88 (s, 2H), 4.77 (s, 3H)
4	2-MeO–C_6H_4	Flash	34	98.02	225.1	7.93 (dd, $J = 7.83$, 1.57 Hz, 1H), 7.52 (m, 1H), 7.07 (m, 2H), 4.78 (s, 2H), 3.97 (s, 3H)
5	4-F–C_6H_4	Flash	55	98.34	213.0	8.07 (m, 2H), 7.20 (m, 2H), 4.77 (s, 2H)
6	3-F–C_6H_4	Flash	79	99.06	213.0	7.87 (d, $J = 7.8$ Hz, 1H), 7.78 (m, 1H), 7.51 (m, 1H), 7.28 (m, 1H), 4.78 (s, 2H)
7	2-F–C_6H_4	Flash	45	98.78	213.0	8.06 (m, 1H), 7.55 (m, 1H), 7.31 (m, 1H), 4.79 (s, 2H)
8	4-Cl–C_6H_4	Flash	52	98.48	229.0	8.02 (d, $J = 9.0$ Hz, 2H), 7.51 (d, $J = 9.0$ Hz, 2H), 4.77 (s, 2H)
9	3-Cl–C_6H_4	Flash	66	99.35	229.0	8.07 (m, 1H), 7.97 (m, 1H), 7.53 (m, 1H), 7.47 (m, 1H), 4.77 (m, 1H)

10	2-Cl–C_6H_4	HPLC[b]/ Flash	36/ 39	98.15	228.9	8.00 (dd, $J = 7.8$, 2.0 Hz, 1H), 7.56 (m, 1H), 7.49 (ddd, $J = 7.7$, 7.7, 1.8 Hz, 1H), 7.42 (ddd, $J = 7.4$, 1.2, 1.2 Hz, 1H), 4.80 (s, 2H)
11	2-CF_3–C_6H_4	Flash	10	99.99	263.0	8.05 (m, 1H), 7.87 (m, 1H), 7.72 (m, 2H), 4.78 (s, 2H)
12	4-Me_2N–C_6H_4	Flash	53	97.89	238.0	7.90 (d, $J = 9.0$ Hz, 2H), 6.72 (d, $J = 9.0$ Hz, 2H), 4.74 (s, 2H), 3.06 (s, 6H)
13	4-*t*-Bu–C_6H_4	HPLC[b]	83	96.87	251.0	7.99 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 8.6$ Hz, 2H), 4.77 (s, 2H), 1.35 (s, 9H)
14	4-Ph–C_6H_4	Filtration[c]	67	94.61	270.9	8.14 (d, $J = 9.0$ Hz, 2H), 7.75 (d, $J = 9.0$ Hz, 2H), 7.64 (d, $J = 7.0$ Hz, 2H), 7.48 (t, $J = 7.4$ Hz, 2H), 7.41 (m, 1H), 4.80 (s, 2H)
15	2-Naphthyl	Filtration[c]	61	95.52	244.9	8.58 (s, 1H), 8.14 (dd, $J = 8.6$, 1.6 Hz, 1H), 7.97 (m, 2H), 7.90 (d, $J = 7.0$ Hz, 1H), 7.59 (m, 2H), 4.82 (s, 2H)

[a]Determined by HPLC analysis @ 254 nm.
[b]Purified on reverse-phase semi-preparative HPLC.
[c]Reaction was diluted with methanol, filtered and air-dried.

EXPERIMENTAL

Typical Experimental Procedure for the Microwave-Assisted Synthesis

Benzoic hydrazide (0.214 g, 1.57 mmol) was placed in a Smith Process Vial[a] (3 mL glass vessel) followed by the addition of 1-chloro-2,2,2-trimethoxyethane (1 mL). The vial was sealed and the mixture was heated in the Emrys Optimizer [11] microwave at 160°C for 300 sec, fixed hold time on, absorption level normal, pre-stirring 10 sec. It was then cooled to room temperature, diluted with 2 mL of methanol and purified by semi-prep HPLC. The HPLC fractions were evaporated under reduced pressure to furnish 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole as a white solid (0.170 g, 55%)

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