An efficient solid-phase synthesis of 3-substituted and 3,3-disubstituted 1,2-dialkylpyrazolidine-3,5-diones†

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An efficient and regioselective procedure for the synthesis of di-, tri- and fully-substituted pyrazolidine-3,5-diones on a solid-phase format is described. Microwave irradiation provided significant rate enhancement in this protocol. To demonstrate the versatility of this chemistry, a representative set of 25 compounds was prepared.

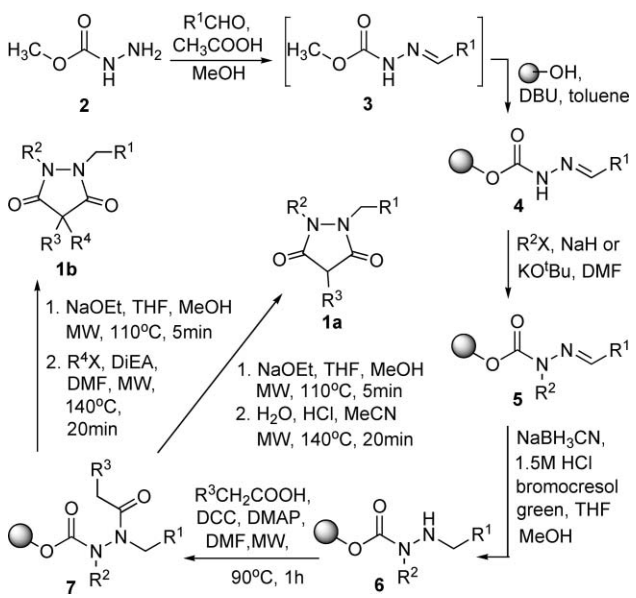
Introduction

Antibiotic resistance in pathogenic bacteria, in particular, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium* and *Streptococcus pneunoniae* is a serious public health threat because of the growing rates of development of resistance of these organisms to traditional antibiotics.[1] There is thus an urgent need to develop new structural classes of compounds with new mechanisms of action to facilitate novel therapeutic approaches for the treatment of infections caused by multiresistant pathogens.

1,2-Diarylpyrazolidine-3,5-diones have been recently described as a novel antibacterial class showing potent and specific inhibition to MurB and good activity against some strains of antibiotic-resistant bacteria.[2] Earlier studies of these compounds have also resulted in the development of phenylbutazone (tradename Butazolidine), oxyphenbutazone (tradename Tandearil), ketazone and sulfinpyrazone (tradename Anturane) as drugs used for the treatment of fever, inflammation, arthritis and gout.[3] Accordingly, several approaches for the synthesis of pyrazolidine-3,5-diones **1** have been described in the literature. Amongst them, the reaction of hydrazines with malonic acid or its derivatives is the most popular method for the direct construction of **1**.[4] However the reaction conditions for these condensations are generally not mild, often requiring either long reaction times (up to a few days), high temperatures (150 °C) or expensive and uncommon reagents. Furthermore, attempts to decorate the pyrazolidine-3,5-dione scaffold by substituting the N1, N2 or C4 positions led to poor selectivity because of the similar reactivities of these positions.[5]

An alternative strategy involves a four-step procedure for the synthesis of polysubstituted **1** from ethyl 3-benzylidenecarbazate. Although this synthesis protocol is a few steps longer than the aforementioned method, it uses common reagents and the stepwise process results in a regiospecific alkylation of the N1 and N2 positions.

To facilitate SAR and the development of **1** as small-molecule probes to biological processes, a flexible and convenient synthetic strategy is desired. We envisage that a solid-phase synthetic protocol which allows convenient handling and distribution of the synthetic intermediates would offer an alternative pathway to generate a diverse set of **1**. To our knowledge, there are no earlier reports of the traceless solid-phase synthesis (SPS) of **1**. Hence we have carefully investigated the aforementioned four-step procedure on solid-phase and herein present an ameliorated and convenient protocol for the synthesis of **1** (Scheme 1) in good yields and high purity.



Scheme 1 SPS of pyrazolidine-3,5-diones.

Results and discussion

For the synthesis of resin **4**, we had initially intended to treat the Wang resin with methyl carbazate **2** to form the resin bound carbazate which would then be reacted with an aldehyde. However the reaction between Wang resin and **2** did not proceed as desired because of the self-condensation of **2**. To circumvent this problem, we reversed the reaction steps and first treated compound **2** with an equimolar amount of aldehyde in methanol. The reaction

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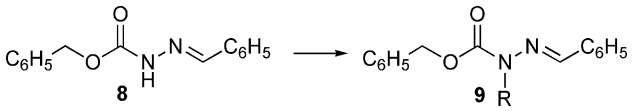
† Electronic supplementary information (ESI) available: Analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all compounds. See DOI: 10.1039/b802648c

Table 1 Solution-phase investigation of the alkylation of **8**



Base	Alkylating agent[a]	Solvent	Reaction conditions	Yield (%)[b]
TEA	**A**, **B** or **C**	CH_2Cl_2 or THF	rt or reflux	0
DiEA				0
Urea	**B**	Acetone	Reflux	0
TMG				0
DBU	**A** or **B**	Acetone	Reflux	Trace
t-BuOK	**C**	*t*-BuOH & THF	rt, 2h	58
t-BuOK	**C**	THF or DMF	rt, 2h	92
t-BuOK	**A** or **B**		rt, 12h	22–47
NaH	**C**		rt, 2h	60
NaH	**A** or **B**	DMF	rt, 12h	76–86

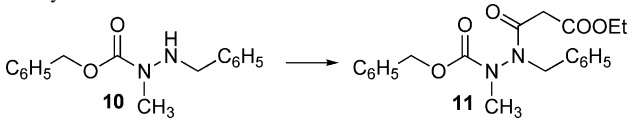
[a] **A** = BnBr, **B** = $BrCH_2COOEt$, **C** = CH_3I. [b] isolated yield of **9**.

proceeded smoothly and gave methyl 3-benzylidenecarbazate **3** as a white solid in 85–90% yield.

The crude **3** was loaded directly onto the Wang resin and the reaction was monitored by KBr FTIR which showed the disappearance of the OH stretch at 3566.0 cm^{-1} and the appearance of a strong ester stretch at 1739.6 cm^{-1}. Resin **4** was subsequently substituted using different alkylating agents to afford resin **5**. Since this reaction is not amenable to FTIR monitoring, solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications required for solid-phase synthesis (Table 1). Attempts to carry out the alkylation using amine bases did not provide the desired product and the starting material was recovered. However the reaction worked well with *t*-BuOK and NaH. Interestingly, we realized that alkylation with CH_3I in the presence of *t*-BuOK gave a better yield than NaH whilst the reverse was true for other alkylating agents, such as benzyl bromide, propyl bromide or allyl bromide. This may be attributed to the strength of the base and alkylating ability of the reagent—it appears that a strong alkylating agent such as CH_3I and a strong base (NaH) would provide too harsh a reaction condition which resulted in the formation of byproducts. On the contrary, a weaker alkylating agent would require NaH to facilitate the reaction. Thus in our solid-phase synthesis, two alkylation conditions were used depending on whether the alkylating agent was CH_3I or any other halide. With resin **5** in hand, we proceeded to reduce the imine using $NaBH_3CN$ and 1.5 M HCl. No premature cleavage of the compound from the resin was observed under this slightly acidic reaction condition. The reaction was monitored by KBr FTIR which showed the appearance of a NH stretch at 3299.1 cm^{-1} in resin **6**.

Lawton *et al.* had earlier reported that dialkyl carbazates could be acylated with ethoxycarbonylacetyl chloride to provide diacyl hydrazines in good yields.[6] However when we applied the reaction to dialkyl carbazate **10**, the desired diacyl hydrazine **11** was not obtained (Table 2). Changing the base and reaction conditions, at best, gave **11** in low yields. Thus, we proceeded to investigate

Table 2 Solution-phase investigation of the synthesis of **11**



Base	Acylating agent[a]	Solvent	Reaction conditions	Yield (%)[b]
—	**A**	THF	0 °C, rt or reflux	0
TEA	**A**	CH_2Cl_2, THF or toluene	0 °C, rt or reflux	0
DiEA	**A**	CH_2Cl_2 or THF	rt or reflux	0
DBU	**A**	CH_2Cl_2 or THF	rt or reflux	0
t-BuOK	**A**	*t*-BuOH and THF	rt	47
t-BuOK	**A**	DMSO	rt	0
NaH	**A**	DMF	rt	0
BuLi	**A**	THF	−76 or rt	0
—	**B**, DMAP, DCC	DMF	rt, 12 h	69
—	**B**, DMAP, DCC	DMF	rt, 48 h	69
DiEA	**B**, EDC	DMF	rt, 12 h	40
DiEA	**B**, DMAP, EDC	DMF	rt, 12 h	54
—	**B**, DMAP, DCC	DMF	MW, 1 h, 60 °C	91
—	**B**, DMAP, DCC	DMF	MW, 1 h, 90 °C	94
—	**B**, DMAP, DCC	DMF	MW, 1 h, 120 °C	85

[a] **A** = EtO_2CCH_2COCl, **B** = EtO_2CCH_2COOH. [b] isolated yield of **11**.

the synthesis of **11** using ethyl hydrogen malonate under different reaction conditions and found that excellent yield was obtained when the reaction mixture was microwave irradiated at 90 °C for 1 h. We applied this reaction condition to the acylation of resin **6** with ethyl hydrogen malonate, cyanoacetic acid and 4-nitrophenylacetic acid to obtain resin **7**. Subsequently, resin **7** was treated with NaOEt in EtOH and THF to give the 4-substituted pyrazolidine-3,5-diones **1a** (R^3 = COOEt, CN, *p*-$NO_2C_6H_5$). Under microwave irradiation at 110 °C, the cyclization was completed within 5 min whilst conventional reflux conditions required 30 min. The crude compound **1a** (R^3 = COOEt) obtained could be further reacted with catalytic amounts of dilute HCl to afford compound **1a** (R^3 = H). Interestingly, under microwave irradiation at 140 °C, the reaction was completed in 5 min whereas by conventional heating, the reaction needed 3 h to complete. It is worth noting that compound **1a** (R^3 = H) could also be obtained directly from resin **7** (R^3 = COOEt) by treating the latter with TFA–CH_2Cl_2 at room temperature for 3 h. Although the yields obtained were generally good (70–75%), compared to the one-pot stepwise cyclization–decarboxylation reaction, the overall yield for the latter was higher.

Finally, we have also prepared 4,4-disubstituted pyrazolidine-3,5-dione, **1b**, from resin **7** in a one-pot manner by treating the crude compound **1a** (R^3 = COOEt, CN, *p*-$NO_2C_6H_5$) with different alkylating agents in the presence of a base. Various bases were tested and DiEA gave better results than TEA, DBU, Li_2CO_3 or NaOEt. Under microwave irradiation, the reaction time was also significantly reduced from 16 h to 20 min.

To illustrate the versatility of this chemistry, a representative set of 25 di-, tri- and tetrasubstituted pyrazolidine-3,5-diones was prepared (Fig. 1). To avoid ester hydrolysis, compound **1a3** was prepared from resin **7** (R^1 = C_6H_5, R^2 = CH_2COOEt, R^3 = COOEt) *via* the acid cyclization–decarboxylation method. The overall yields obtained were 28–65%, indicating that the average yield for each step was 80–92%.

Conclusion

In summary, an efficient and regioselective traceless SPS of 1,2-dialkylpyrazolidine-3,5-diones, its 3-substituted and 3,3-disubstituted derivatives have been devised. Using microwave irradiation, we have also shown that the total reaction time could be considerably shortened. Since a variety of reagents can be used in each step of the reaction, the overall strategy enables efficient library generation.

Experimental

General methods

^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 or Bruker DPX 500 Fourier Transform spectrometer. Chemical shifts are reported in δ (ppm), relative to the internal standard of tetramethylsilane (TMS). All infrared (IR) spectra were recorded on a Bio-Rad FTS165 spectrometer. Mass spectra were performed on a VG Micromass 7035 spectrometer under electron impact (EI), Finnigan MAT LCQ under electrospray ionization (ESI, normal) and Finnigan MAT 95XL-T under electrospray ionisation (ESI, accurate). Wang resin was purchased from Tianjin Nankai Hecheng Science and Technology Co (100–200 mesh, loading: 1.4 mmol g^{-1}, Catalog no. HCW02-1-1). All chemical reagents were obtained from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70–230 mesh). The solid-phase room temperature reactions were agitated on a Stuart Scientific SF1 flask shaker. The microwave-assisted reactions were performed in sealed microwave reactors using the Biotage Initiator and ramp was set as "High".

General experimental procedures

Preparation of methyl 3-alkylidenecarbazate (3). To a solution of methyl carbazate (2.7 g, 30 mmol) in MeOH (AR grade, 30 mL) was added the respective aldehyde (30 mmol) and glacial acetic acid (0.3 mL) (for benzaldehyde HOAc was unnecessary). The mixture was stirred at room temperature for 30 min and then concentrated. The resulting white solid obtained was dried in a vacuum oven and used without further purification.

Preparation of 3-alkylidenecarbazate resin (4). Wang resin (5.0 g, 7 mmol) was swelled in toluene (40 mL) for 30 min. Thereafter compound **3** (14 mmol) and DBU (0.32 mL, 2.1 mmol) were added and the mixture was refluxed for 24 h. When the mixture had cooled, the resin was filtered, washed with DMF (20 mL × 3), H_2O (20 mL × 3), EtOH (20 mL × 3), CH_2Cl_2 (20 mL × 3), Et_2O (20 mL × 3) and dried overnight at 50 °C in a vacuum oven.

Preparation of 3-alkylidene-2-substituted carbazate resin (5). Resin **4** (2.0 g, 2.213 mmol) was swelled in DMF (15 mL) for 30 min. Thereafter *t*-BuOK (0.4970 g, 4.426 mmol) [or NaH (60% dispersion in mineral oil, 0.177 g, 4.426 mmol)] was added and the mixture was shaken at room temperature for 1 h. Subsequently the mixture was cooled in an ice–water bath and CH_3I (0.4 mL, 6.639 mmol) [or RX (other alkylating agents, 6.639 mmol)] was added dropwise. The mixture was then shaken at room temperature for another 12 h. Thereafter, the resin was filtered, washed with DMF (20 mL × 3), H_2O (20 mL × 3), EtOH (20 mL × 3), CH_2Cl_2 (20 mL × 3), Et_2O (20 mL × 3) and dried overnight at 50 °C in a vacuum oven.

Preparation of 2,3-disubstituted carbazate resin (6). To a suspension of resin **5** (2.0520 g, 2.213 mmol) in MeOH (8 mL) and THF (13 mL) was added $NaBH_3CN$ (0.4170 g, 6.639 mmol) and bromocresol green indicator (half a spatula). 1.5 M HCl was then added dropwise to just maintain the yellow color of the solution. When the yellow color persisted for 1 h without further addition of acid, the resin was filtered, washed with DMF (20 mL × 3), H_2O (20 mL × 3), EtOH (20 mL × 3), CH_2Cl_2 (20 mL × 3), Et_2O (20 mL × 3) and dried overnight at 50 °C in a vacuum oven.

Preparation of 3-alkanoyl-2,3-disubstituted carbazate resin (7). Resin **6** (1 g, 1.1 mmol) was swelled in DMF (10 mL) for 30 min. Thereafter, the respective substituted acetic acids (2.2 mmol), DCC (0.4540 g, 2.2 mmol) and DMAP (0.0400 g, 0.33 mol) were added in the stated order. The mixture was heated under microwave irradiation by ramping up the reaction to 90 °C within 5 min and holding the reaction at this temperature for 1 h. When the mixture had cooled, the resin was filtered, washed with DMF

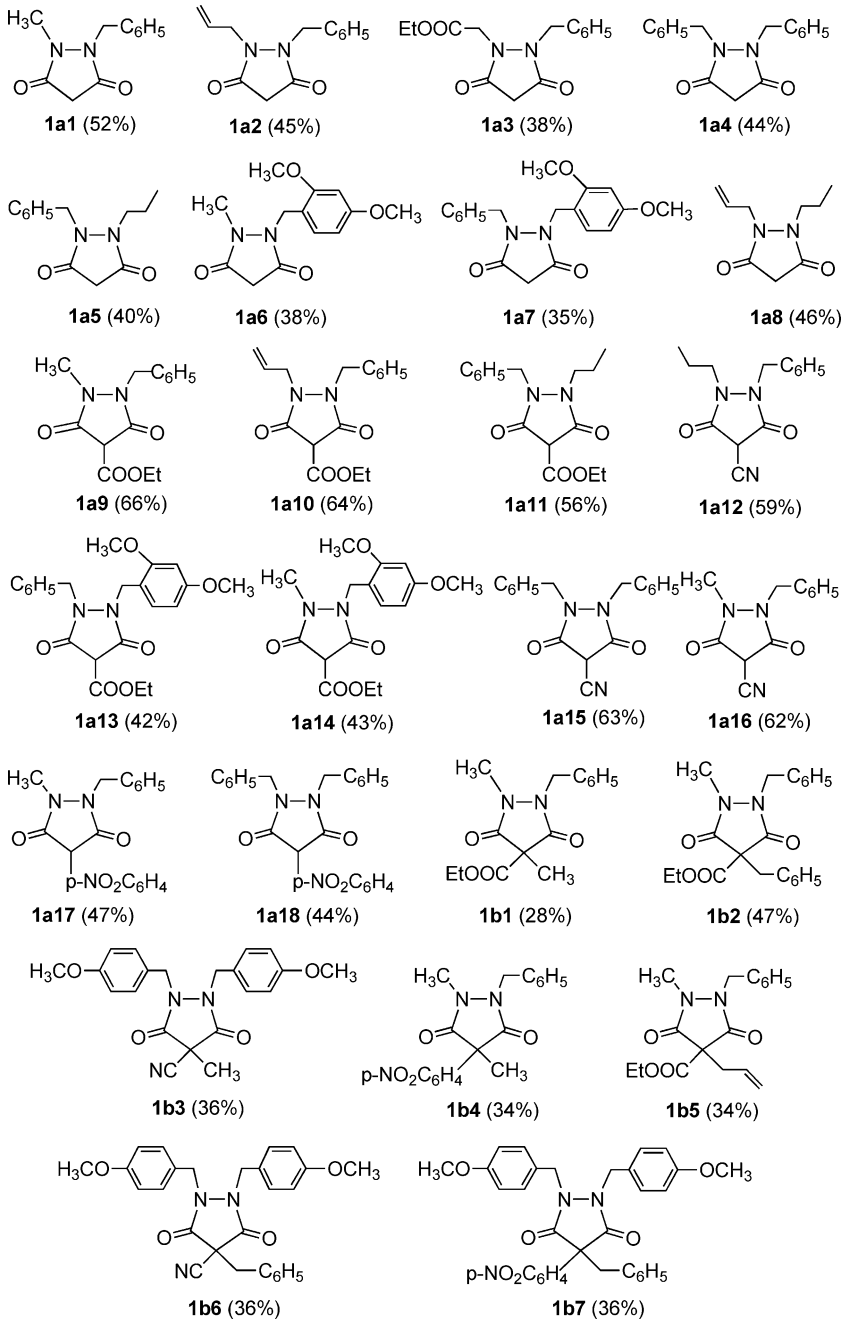


Fig. 1 Library of pyrazolidine-3,5-diones.

(20 mL × 3), H_2O (20 mL × 3), EtOH (20 mL × 3), CH_2Cl_2 (20 mL × 3), Et_2O (20 mL × 3) and dried overnight at 50 °C in a vacuum oven.

Preparation of 4-ethoxycarbonyl-1,2-disubstituted pyrazolidine-3,5-dione (1a, R^3 = COOEt). A mixture of resin **7** (1.100 g, 1.1 mmol, R^3 = COOEt), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. The resin was then filtered and washed with MeOH (10 mL × 3). The combined filtrate was concentrated and purified by column chromatography (EtOAc : hexane = 1:1, MeOH : CH_2Cl_2 = 1 : 5) to give compound **1a** (R^3 = COOEt).

Preparation of 4-cyano- or (4-nitro)phenyl- 1,2-disubstituted pyrazolidine-3,5-dione (1a, R^3 = CN or *p*-$NO_2C_6H_5$). A mixture of resin **7** (1.100 g, 1.1 mmol, R^3 = CN or *p*-$NO_2C_6H_5$), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. Thereafter, the resin was filtered and washed with MeOH (10 mL × 3). The combined filtrate and washing was concentrated, diluted with H_2O and, extracted with ether. The aqueous layer was acidified with 1.5 M HCl and the solid which precipitated was collected and washed with H_2O to give compound **1a** (R^3 = CN or *p*-$NO_2C_6H_5$). If no precipitate formed, the acidified aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 extract was dried with $MgSO_4$, filtered,

concentrated to dryness to give compound **1a** (R^3 = CN or *p*-$NO_2C_6H_5$).

Preparation of 1,2-disubstituted pyrazolidine-3,5-dione (1a, R^3 = H). *Method A*—A mixture of resin **7** (1.100 g, 1.1 mmol, R^3 = COOEt), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. After the mixture has cooled, it was acidified with 1.5 M HCl and concentrated. To the resulting solid was added MeCN (10 mL), H_2O (10 mL) and a few drops 1.5 M HCl. The mixture was heated under microwave irradiation at 140 °C for 5 min, filtered and washed with MeOH (10 mL × 3). The combined organic layer was concentrated and purified by column chromatography (EtOAc : hexane = 1 : 1) to give compound **1a** (R^3= H). *Method B*—Resin **7** (0.500 g, 0.5 mmol, R^3 = COOEt) was swelled in CH_2Cl_2 (25 mL) for 30 mins. TFA (10 mL) was then added dropwise and the suspension was shaken at room temperature for 3 h. Thereafter, the resin was filtered and washed with CH_2Cl_2. The combined filtrate and washing was concentrated and purified by column chromatography to give compound **1a** (R^3 = H).

Preparation of 1,2,4,4-tetrasubstituted pyrazolidine-3,5-dione (1b). A mixture of resin **7** (1.100 g, 1.1 mmol), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. After which, it was concentrated and dried. The resulting residue was diluted with DMF (10 mL), and DiEA (1.14 mL, 6.6 mmol) and CH_3I (0.21 mL, 3.3 mmol) were added. The reaction mixture was heated under microwave irradiation at 140 °C for 20 min. Thereafter, the resin was filtered and washed with MeOH (10 mL × 3). The combined filtrate and washing was concentrated and purified by column chromatography (EtOAc : hexane = 1 : 3) to give compound **1b**.

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