Pergamon

Tetrahedron Letters 41 (2000) 1889–1893

TETRAHEDRON LETTERS

Novel applications of carbon dioxide/MeOH for the synthesis of hydantoins and cyclic ureas via the Ugi reaction

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Received 6 December 1999; accepted 4 January 2000

Abstract

This communication reveals novel applications of the CO_2/MeOH reagent combination coupled with the UDC (Ugi/DeBOC/Cyclize) strategy. The Ugi five component condensation (5CC) affords carbamate protected amino-amides in good yield. When one of the supporting reagents employed in the Ugi reaction possesses a tethered amino-BOC protected functional group, subsequent acid treatment and proton scavenging results in rapid cyclization to cyclic ureas. Additionally, treatment of the 5CC product with base affords hydantoins in good yield, representing a novel and short approach to this class of molecule.

With the recent emergence of combinatorial chemistry and high speed parallel synthesis in the lead discovery arena, the multi-component reaction (MCR) has witnessed a resurgence of interest.[1] Easily automated one-pot reactions, such as the Ugi[2] and Passerini[3] reactions, are in fact powerful tools for producing diverse arrays of compounds, often in one step and high yield. Despite this synthetic potential, the Ugi reaction is limited by producing products that are flexible and peptidic-like, often being classified as 'non-drug-like'. Interestingly, several novel intramolecular variations on the Ugi reaction have recently been reported where constrained, more biologically relevant products result from interception of the intermediate nitrilium ion using a bifunctional input.[4] An alternative approach is to constrain the Ugi product via a post-condensation modification after initial formation of the classical Ugi product.[5,6]

This letter reveals a series of novel applications of the CO_2/MeOH, **1**, reagent combination in the Ugi 5CC (five component condensation). Utilizing UDC (Ugi/De-BOC/Cyclization) methodology, diverse arrays of cyclic ureas with core templates, **2**, are readily available (Scheme 1). Additionally, a facile and novel synthesis of hydantoins of generic structure, **3**, is reported via base treatment of the Ugi 5CC product. Reports of the biological utility of cyclic ureas and hydantoins have appeared in several areas, including applications as inhibitors of integrins and kinases.[7]

The Ugi 5CC was originally reported in 1961[8] and only two further reports of this reaction have appeared since that date.[9] The reaction consists of the condensation of an aldehyde (or ketone), amine,

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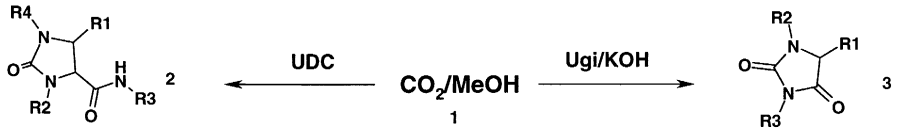
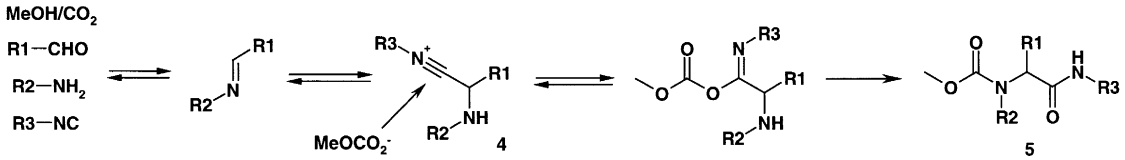
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00053-8



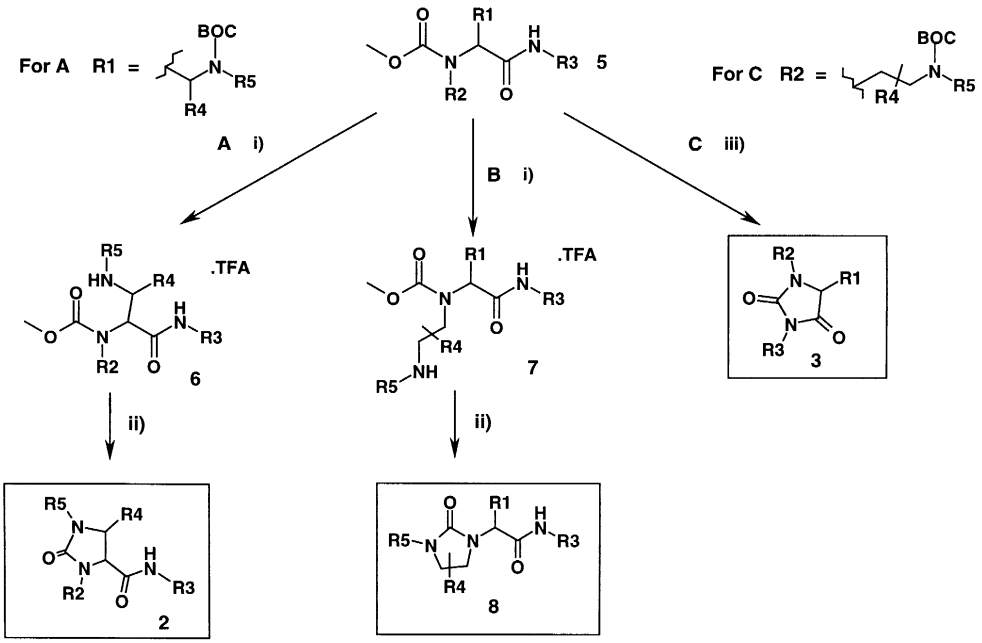
Scheme 1.

isonitrile, methanol and CO_2. Recent investigations by Armstrong[9] have, however, extended the scope of this condensation via the use of CS_2 and COS as oxidized carbon sources. The generally accepted mechanism for this rarely used reaction is shown in Scheme 2. The key step is addition of methyl carbonic acid (generated from CO_2 and methanol) to the intermediate nitrilium ion, **4**. An irreversible acyl transfer step subsequently drives the reaction to completion giving the carbamate, **5**, in good yield. Area% (A%) yields for **5** (LC/MS as judged by ELS-evaporative light scattering detection and UV detection) are reported in Table 1.



Scheme 2.

Incorporation of a BOC protected internal nucleophile at R_1 or R_2 and subsequent synthetic manipulation affords the desired constrained ureas **2** and **9**, (Scheme 3). For example, *N*-BOC-α-amino aldehydes[10] perform well in the 5CC and acid treatment of the Ugi product, **5**, with a 10% TFA solution in dichloroethane gives the TFA salt, **6**.



Scheme 3. Reagent and conditions. (i) 10% Trifluoroacetic acid in dichloroethane. (ii) Na_2CO_3 (sat.). (iii) 1N KOH in MeOH:THF:H_2O, 3 days, then cHCl

Base treatment, either with a H^+ scavenger (MP-carbonate or PS-*N*-methyl morpholine) or a saturated solution of sodium carbonate, with subsequent reflux in methanol, affords cyclic ureas of general structure, **2**, in good yield, (Table 1). The reaction is general for both a range of commercially available primary amines [e.g., with attached alkyl, aryl, heteroaryl, acidic and basic functionality] and isonitriles.

Area% yields of cyclic products, **9**–**18**, ranged from 25% to 83%. Interestingly, a consistent major side product was observed in this series resulting from elimination of NH_3 [MH^+=M_r **7**-NH_3]. Application of the UDC strategy with *N*-BOC diamines generates TFA salts of general structure, **7**, however, cyclization to cyclic urea, **8**, under similar conditions was sluggish. Area% yields were observed only in the 5–10% range for examples, **19**–**21** (reflux, MeOH, 3 days) and further study was discontinued.

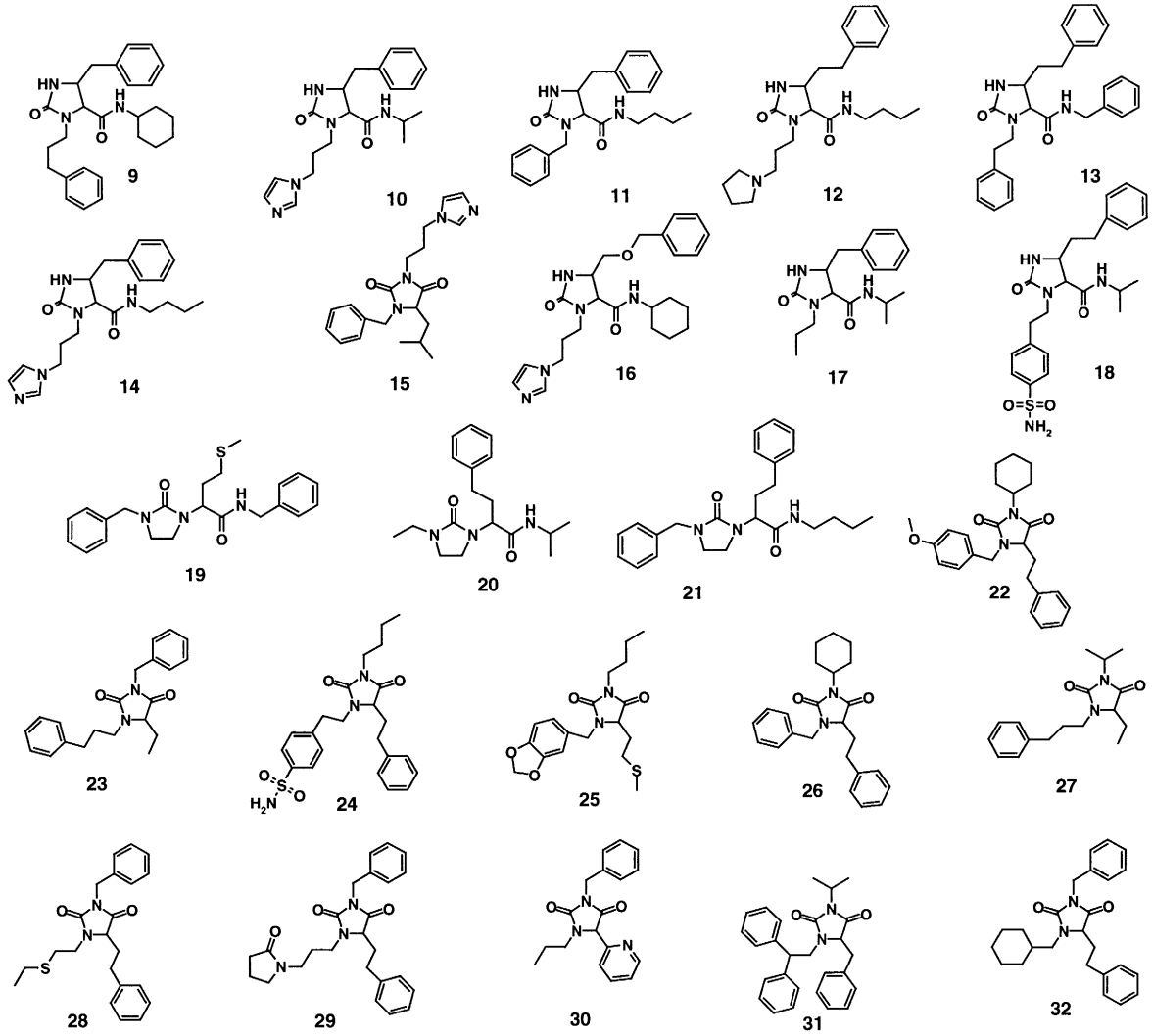


Table 1

Cpd #	A%	Ugi A%	Cpd #	A%	Ugi A%	Cpd #	A%	Ugi A%
9	83%/60%	100%/100%	17	70%/50%	100%/95%	25	40%/30%	43%/35%
10	55%/42%	100%/100%	18	63%/49%	100%/95%	26	95%/90%	88%/80%
11	50%/40%	100%/100%	19	< 10%	64%/43%	27	65%/60%	77%/70%
12	48%/26%	100%/100%	20	< 10%	80%/61%	28	65%/40%	83%/50%
13	75%/25%	80%/67%	21	< 10%	80%/67%	29	100%/58%	100%/62%
14	38%/32%	100%/100%	22	80%/70%	91%/80%	30	100%/58%	100%/44%
15	72%/57%	93%/81%	23	60%/70%	90%/78%	31	87%/72%	88%/53%
16	25%/13%	100%/81%	24	70%/60%	100%/100%	32	100%/87%	100%/70%

Elution conditions :- 0 - 0.1% TFA H_2O/CH_3CN 10% to 100%, 5 min. run. A% = area % purity of final product as judged by lc/ms where X%/Y% = ELS detection %/UV220 detection % (ELS = evaporative light scattering). Ugi A% = area% purity of the initial Ugi condensation product as judged by lc/ms where X%/Y% = ELS%/UV220%.

A recent publication by Ugi prompted further study of the CO_2/MeOH reagent combination.[11] In this article, Ugi revealed a novel application of the U-5C-4CR (Ugi-5-centre-4-component reaction) applied to the synthesis of 2,6-piperazine-diones.[11] The internal nucleophile in this example was the amidic NH derived from the isonitrile input. It was thus envisioned that applying this strategy to the Ugi 5CC with the CO_2/MeOH reagent combination would allow access to hydantoins of general structure, **3**, containing three potential diversity points. Noteworthy is the recent interest in producing libraries based on this biologically versatile template.[12] Simply treating the 5CC products of generic structure, **5**, with KOH in MeOH, followed by acidification and filtration of KCl, successfully produced a variety of fully functionalized hydantoins in good yield (Table 1). A% yields (ELS) for examples, **22**–**32**, range from 40%–100%.[13]

In summary, two novel applications of the CO_2/MeOH reagent combination have been reported. Firstly, applying UDC methodology allows access to cyclic ureas of general structure, **2**, in good yield. Interestingly, utilization of the amidic NH of **5** as an internal nucleophile, allows the facile synthesis of arrays of hydantoins with three diversity points. This short two step solution phase synthesis compares well with currently reported procedures.[12]

Acknowledgements

We would like to thank Beth Capp (Library Services).

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13. For general experimental procedure for hydantoin synthesis: Benzylamine (0.75 mmol, 1 equiv.) and cyclohexylisonitrile (0.75 mmol, 1 equiv.) were added to a stirring solution of 3-phenyl-propionaldehyde (0.9 mmol, 1.2 equiv.) in methanol (15 ml) stirring in a Radley's Carousel tube. The reaction mixture was cooled to 0°C, and CO_2 was bubbled into the sealed tube for 5 min. The tube was stirred on the Radley's Carousel under CO_2 atmosphere for 18 h, and the solvent evaporated in vacuo. The crude product was dissolved in methanol (1.5 ml), 0.75 ml (THF) and 0.5 ml (H_2O), followed by 0.03 ml of a 1 g/1 ml solution of KOH in H_2O. The resulting solution was stirred for 72 h. The solutions were acidified with concentrated HCl to pH~2 and evaporated in vacuo. The oily solid was partially dissolved into CH_2Cl_2, and KCl filtered. The filtrate was concentrated in vacuo and purified by column chromatography (hexane:ethyl acetate, 2:1) to yield, **26**, as a clear oil (100 mg, isolated yield 50% for the two step process). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.01–7.03, 7.15–7.34 (2×C_6H_5, 2×m, 10H), 4.81–4.86 (m, 1H), 4.13–4.18 (m, 1H), 3.91–4.02 (m, 1H), 3.76–3.79 (m, 1H), 2.40–2.50 (m, 2H), 2.13–2.23 (m, 2H), 1.68–2.00, 2.13–2.23, 2.40–2.50 (3×m, 6H), 1.21–1.37 (m, 4H). ^{13}C (125 MHz, $CDCl_3$, ppm): 172.68, 156.79, 140.36, 136.00, 128.97, 128.50, 128.35, 128.27, 128.05, 126.24, 57.94, 51.85, 44.98, 30.40, 29.45, 29.16, 25.86, 25.05. MS (TOF MS ES$^+$) 377 (MH^+). A similar procedure was followed for the synthesis of hydantoin **27**, (isolated yield 40% for the two step process). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.16–7.21, 7.25–7.30 (2×m, 5H), 4.26–4.33 (m, 1H), 3.79–3.81 (m, 1H), 3.61–3.78 (m, 1H), 3.00–3.08 (m, 1H), 2.61–2.67 (m, 1H), 1.72–1.77, 1.84–1.96 (2×m, 4H), 1.37–1.40 (m, 6H), 0.74–0.79 (m, 3H). ^{13}C (125 MHz, $CDCl_3$, ppm): 173.18, 156.90, 141.35, 128.90, 128.62, 126.53, 59.38, 44.19, 40.60, 33.55, 29.85, 21.88, 20.18, 19.97, 7.18. MS (TOF MS ES$^+$) 288 (MH^+).