Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information for

Probing the mechanism of the Ugi four-component reaction with charge-tagged reagents by ESI-MS(/MS)

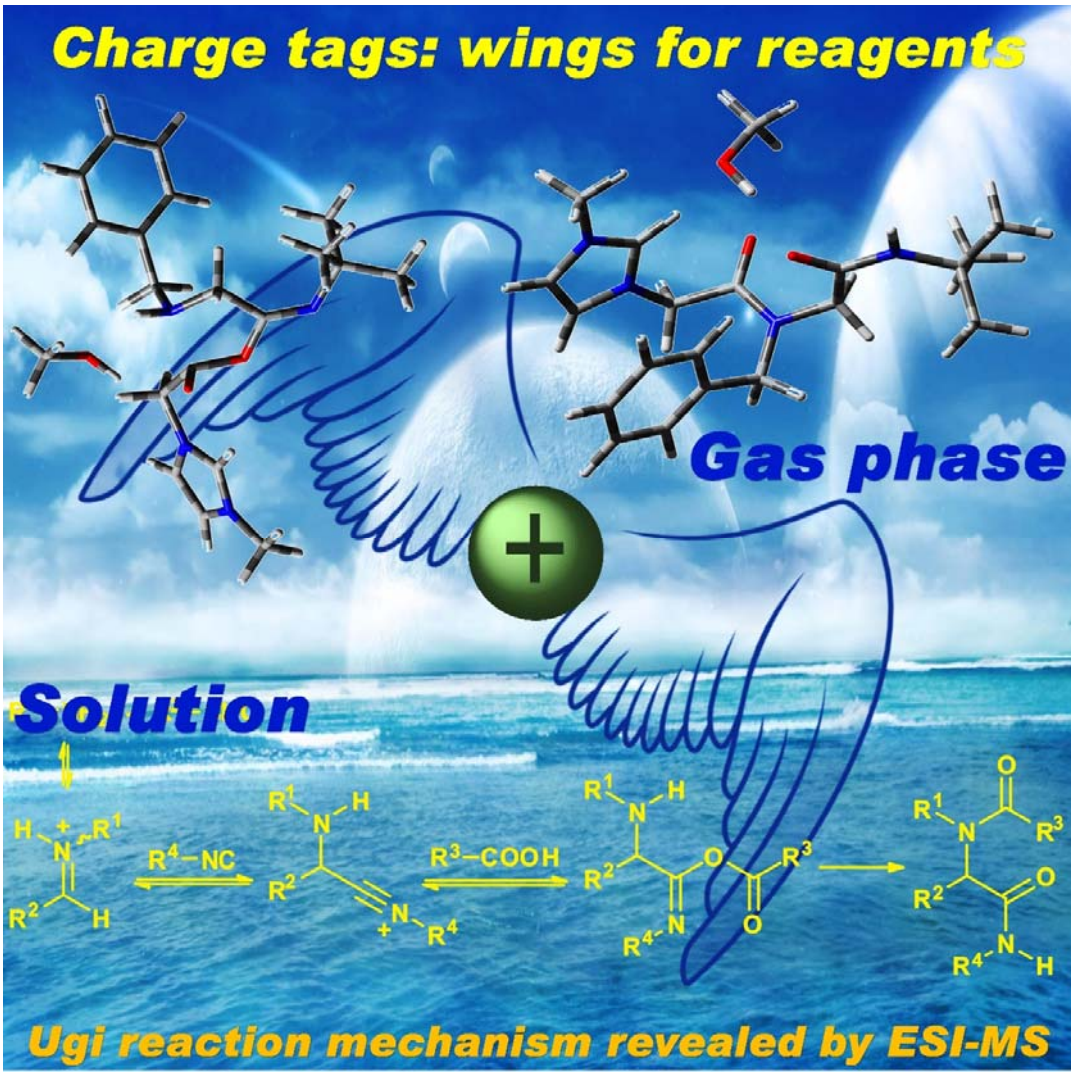
Gisele A. Medeiros,[a] Wender A. da Silva,[a] Giovana A. Bataglion,[b] Davi A. C. Ferreira,[a] Heibbe C. B. de Oliveira,[a] Marcos N. Eberlin,*[b] and Brenno A. D. Neto,*[a]

[a] Laboratory of Medicinal and Technological Chemistry, Chemistry Institute (IQ-UnB), Universidade de Brasilia, Campus Universitário Darcy Ribeiro, CEP 70904-970 – P.O.Box 4478 – Brasília – DF – Brazil.

[b] Laboratory for Bioactive Compounds Synthesis, University of Brasilia (IQ-UnB). Campus Universitário Darcy Ribeiro, CEP 70904970, P.O.Box 4478, Brasilia-DF, Brazil.

[c] ThoMSon Mass Spectrometry Laboratory, University of Campinas-UNICAMP, Campinas, SP, Brazil.

To whom correspondence should be addressed: brenno.ipi@gmail.com, eberlin@iqm.unicamp.br



Mass Spectrometry Experiments

The Ugi four-component reactions were monitored using a Synapt HDMS (High Definition Mass Spectrometry; Waters Corp., Manchester, UK). This mass spectrometer is equipped with an ESI source and it has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-fight geometry (oa-TOF). The reaction mixtures (100 μM) were subjected to ESI, which source conditions were as follows: capillary voltage 3.0 kV, sample cone 30 V, extraction cone 3 V, source temperature 100 °C, desolvation temperature 100 °C and desolvation flow rate 300 mL min^{-1} of N_2. For the MS experiments, trap and transfer cells were operated at 6 and 4 V, respectively. While for MS/MS experiments, the ions of interest were selected in the quadrupole analyzer, fragmented in the transfer cell using argon as collision gas (transfer energy was optimized for each ion of interest) and then the product ions were analyzed by TOF.

Traveling-Wave Ion Mobility Mass Spectrometry (TWIM-MS) experiments were performed in order to identify possible isomeric intermediate of the Ugi four-component reactions. For mobility separation, the TWIM cell was operated at a gas flow ranging 10-62 mL min^{-1} of nitrogen or of carbon dioxide. The parameters wave velocity and height were set to 200-250 ms^{-1} and 30 V, respectively. Independently of the settled gas flow, no separation could be noted for any of the performed experiments.

Theoretical calculations

All electronic structure calculation performed in this work were done within Kohn-Sham Density Functional Theory (DFT) formalism[1, 2] using the M06-2X exchange-correlation[3] functional combined with the large 6-31+G(d,p) and 6-311+G(2d,2p) Pople split-valence basis set for geometries optimizations followed by single point calculations, respectively. The transitions states were optimized using the Berny algorithm.[4] All structures were optimized and frequency calculations were performed to ensure the absence of any imaginary frequencies on local minima, and the presence of only one imaginary frequency on transition states; and were also used to compute zero-point vibrational energy (ZPVE). ZPVE were calculated at 298.15 K and 1 atm. Methanol has been considered as the reaction media (explicit treatment) for calculated structures. Both geometrical and electronic theoretical calculations were carried out using Gaussian 09 program suite.[5]

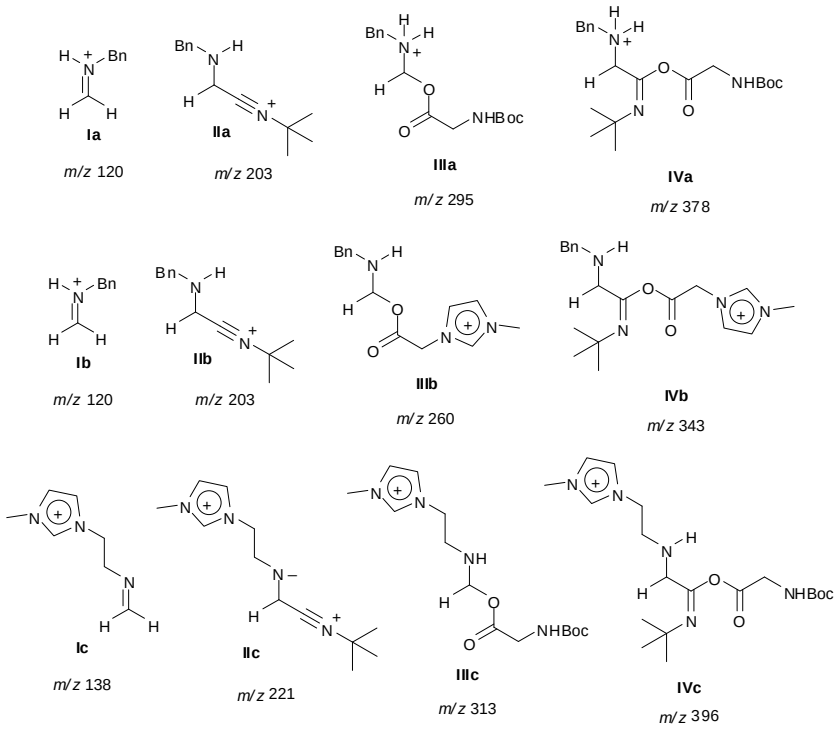


Figure S1. Possible intermediates for the U4CR and their calculated *m/z* ratios.

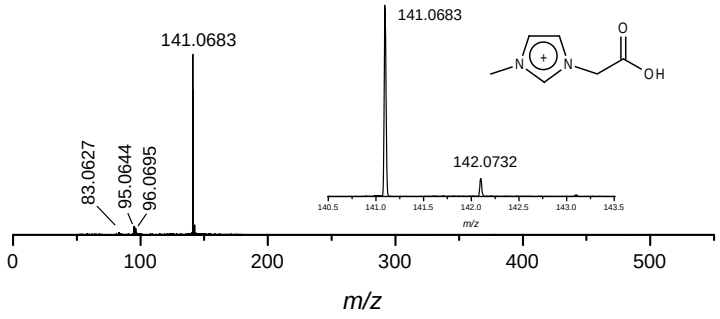


Figure S2. ESI(+)-MS/MS from a methanolic solution of the charge-tagged carboxylic acid 1-methyl-3-carboxymethylimidazolium chloride (**MAI.Cl**). Note that the ion of *m/z* 141 is the cation **MAI**.

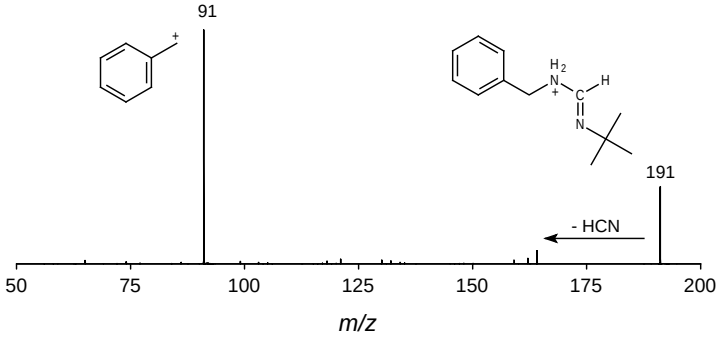


Figure S3. ESI(+)-MS/MS of the signal of *m/z* 191 (a fragment from the signal of *m/z* 247).

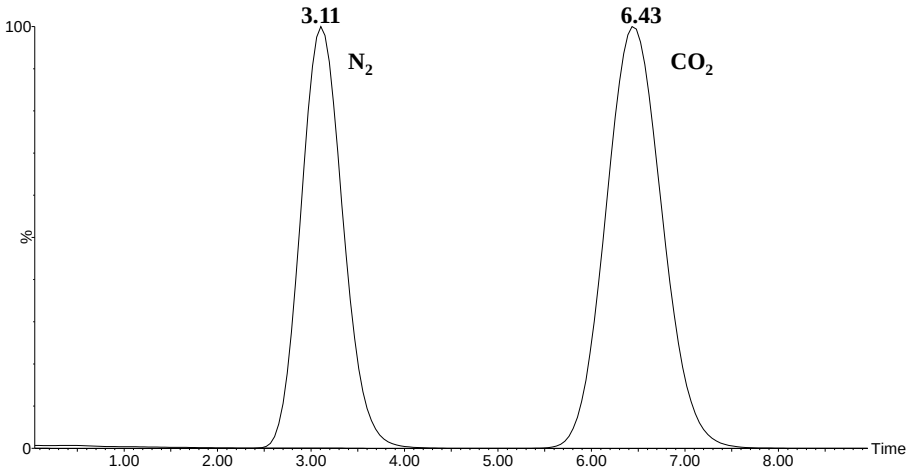


Figure S4. Drift time plots for the ion of *m/z* 343. For N_2 as the drift gas fow: 45 mL min^{-1} (2.19 mbar); wave velocity: 250 ms^{-1} and wave height: 30 V. For CO_2 as the drift gas fow: 50 mL min^{-1} (1.54 mbar); wave velocity: 200 ms^{-1} and wave height: 30 V.

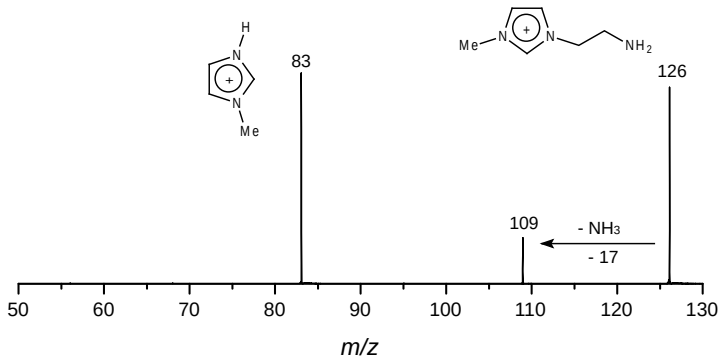


Figure S5. ESI(+)-MS/MS of the signal of the charge-tagged amine.

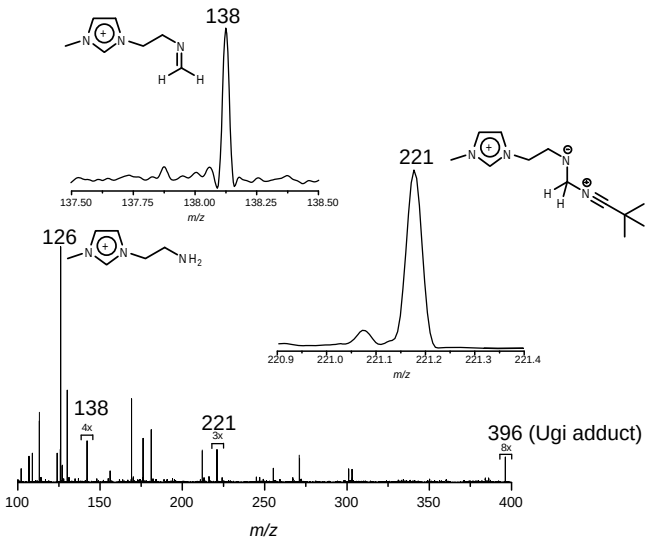
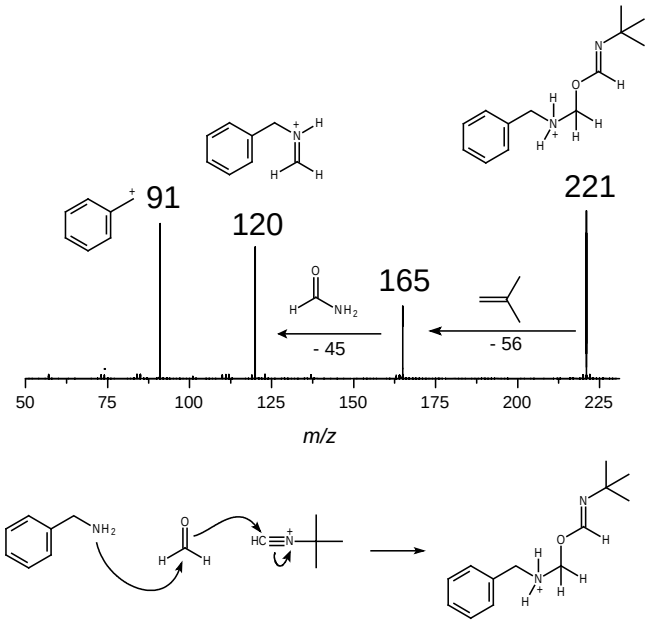


Figure S6. ESI(+)-MS of the Ugi reaction using the charge-tagged amine (*m/z* 126), Boc-glycine, formaldehyde and *t*-butyl isocyanide. The signals of *m/z* 138 and *m/z* 221 could be noted two minutes after the injection and are shown as the insets. Despite their very low intensity, ESI-MS/MS could be acquired for those two ions. Also, note the signals observed are not very intense and many degradations can be observed in the MS spectrum. The very low abundance of the Ugi adduct (*m/z* 396) prevented its ESI(+)-MS/MS to be acquired.



Scheme S1. ESI(+)-MS/MS of the by-product ion of *m/z* 221 and (bottom) a proposal for this side reaction mechanism.

Cartesian coordinates, energies and thermal corrections for all the calculated structures.

Structure IV

E(M06-2X/6-311++g(2d,2p)//M06-2X/6-31+g(d,p))= -1225.10457799 hartree
Zero-point correction = 0.505188 hartree
Thermal correction to Energy at 298.15 K = 0.533734 hartree
Thermal correction to Enthalpy at 298.15 K = 0.534679 hartree
Thermal correction to Gibbs Free Energy at 298.15 K = 0.442091 hartree

Standard orientation:

H	0.93466100	-2.24789900	1.98124100
O	1.48054900	-0.49985900	1.43336400
C	1.04891900	-0.40007700	0.23974000
C	1.78611100	-1.25007400	-0.81104600
H	1.39768000	-1.10728400	-1.82053200
H	1.73625400	-2.30242500	-0.51558800
O	0.95820800	0.92293600	-0.31085400
C	-0.15301100	1.57294400	0.18005600
N	-0.24929700	2.81002600	0.04030900
C	-1.41740400	3.61125600	0.44896100
C	-1.07195000	0.51032900	0.78493600
H	-2.12030500	0.64101200	0.51958500
N	-0.54278200	-0.75580800	0.22022800
C	-1.15033400	-1.12939000	-1.09331100
H	-0.92385500	-0.32371800	-1.79919700
H	-0.64936900	-2.04635300	-1.41686400
H	-0.63552800	-1.54664600	0.88087000
O	0.28640600	-2.91948300	1.69171400
C	0.10323400	-3.93161100	2.67487000
H	1.03437900	-4.47680200	2.85512000
H	-0.26011600	-3.51117800	3.61746100
H	-0.64037900	-4.62935400	2.28809700
C	-2.55259600	3.39540000	-0.55982000
H	-2.20321200	3.60943900	-1.57395400
H	-2.93375500	2.36857900	-0.53149800
H	-3.38682300	4.06551900	-0.33239300
C	-0.95661100	5.07092400	0.38569300
H	-1.78150200	5.74738100	0.62743300
H	-0.14324100	5.24174100	1.09674400
H	-0.58702500	5.30404200	-0.61609100
C	-1.88554000	3.30101600	1.87786000
H	-2.40421100	2.34156200	1.95777400
H	-1.03635800	3.30439200	2.56859800
H	-2.58960700	4.07076500	2.20621900
C	-2.63487100	-1.35657200	-0.97194600
C	-3.53999500	-0.48708200	-1.58231200
C	-3.11103300	-2.43887100	-0.22474600
C	-4.91252600	-0.69348800	-1.44405700
H	-3.17275300	0.34887400	-2.17341600
C	-4.48054600	-2.64175500	-0.08261400
H	-2.40797600	-3.12806700	0.24073300
C	-5.38219900	-1.76778600	-0.69200100
H	-5.61142800	-0.01691600	-1.92462300
H	-4.84599900	-3.48410400	0.49531400
H	-6.44964900	-1.92924300	-0.58463100
N	3.19807000	-0.83114900	-0.84326500
C	4.08392800	-1.18054900	-1.84121200
C	3.83091700	-0.05155600	0.03815700

C	5.27363900	-0.59326400	-1.54461900
H	3.79303000	-1.80682200	-2.66976200
H	3.37275600	0.35665900	0.92964700
H	6.22042100	-0.60878300	-2.06103600
C	6.10875700	0.90295300	0.31516600
H	5.66782800	1.32992100	1.21453700
H	6.94723900	0.26146600	0.58674700
H	6.44295400	1.70465500	-0.34358100
N	5.08965700	0.10595100	-0.37047100
H	-0.95630200	0.48120000	1.86911200

Structure V

E(M06-2X/6-311++g(2d,2p)//M06-2X/6-31+g(d,p))= -1225.16469490 hartree
Zero-point correction = 0.505679 hartree
Thermal correction to Energy at 298.15 K = 0.534558 hartree
Thermal correction to Enthalpy at 298.15 K = 0.535502 hartree
Thermal correction to Gibbs Free Energy at 298.15 K = 0.444464 hartree

Standard orientation:

H	-2.01195500	4.22126400	-0.44536400
H	-0.62606800	4.77807100	0.51068600
H	-1.47631700	3.28937400	0.98965600
C	-1.14487800	3.89363600	0.13788700
O	-0.22509900	3.16986100	-0.67268100
H	-0.65763000	2.34666600	-0.95676700
O	-0.42780300	1.11408500	2.02914100
C	0.13473700	0.05155800	1.80087100
C	1.60846400	-0.08208600	2.19636100
H	1.96442800	-1.10945000	2.26489100
H	1.72574200	0.41973300	3.15895900
O	-1.19234700	0.57158700	-0.89701600
C	-2.14020500	0.01278500	-0.33773600
N	-3.39681300	0.14755300	-0.79959300
C	-4.68665100	-0.49310200	-0.43472900
C	-1.89827600	-0.81386800	0.93014700
H	-2.37850700	-1.79086900	0.85917500
N	-0.48474700	-0.99878600	1.20787400
C	0.16902200	-2.27428600	0.88365500
H	0.43599300	-2.80301400	1.80728300
H	-0.59085300	-2.88645000	0.39055500
H	-3.42194900	0.71627000	-1.63982000
H	-2.34766400	-0.26930800	1.76505100
C	-4.70542200	-1.95408500	-0.89887700
H	-4.53631600	-2.01777000	-1.97728900
H	-3.94053200	-2.55315600	-0.39588300
H	-5.67681400	-2.40375100	-0.67403100
C	-5.75042300	0.29890100	-1.20295100
H	-6.73661700	-0.13599400	-1.02693300
H	-5.77038600	1.34253400	-0.87481900
H	-5.56017600	0.26887900	-2.28115000
C	-4.98343800	-0.38531800	1.06536500
H	-4.80464100	0.63195800	1.42592200
H	-6.03639900	-0.62578200	1.23419300
H	-4.39976800	-1.08638700	1.66562300
N	2.43679200	0.59849500	1.19429700
C	3.73412100	0.26456500	0.87256400
C	2.04346400	1.61646500	0.42289600
C	4.12380000	1.11162100	-0.11841100
H	4.25065200	-0.55348300	1.34945500

H	1.07007000	2.10224800	0.41588700
H	5.05349000	1.18492600	-0.66011200
N	3.05435400	1.93958200	-0.38090300
C	3.00051100	3.00314000	-1.38886400
H	1.98535900	3.40355500	-1.39896100
H	3.71659000	3.78319400	-1.12869800
H	3.24504500	2.57882300	-2.36317000
C	1.38289000	-2.18232300	-0.02335300
C	1.40098500	-1.32939100	-1.13220400
C	2.47900000	-3.01302100	0.22064700
C	2.50274400	-1.32215000	-1.98579600
H	0.55419300	-0.67354300	-1.31878600
C	3.57836800	-3.00928100	-0.63998500
H	2.47008100	-3.68364500	1.07772500
C	3.59085000	-2.16386300	-1.74667800
H	2.50226900	-0.66875600	-2.85371600
H	4.41634100	-3.67184400	-0.44796800
H	4.43925300	-2.16584000	-2.42372200

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