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Mendeleev Commun., 2016, **26**, 69–71
Mendeleev Communications

An easy one-step synthesis of imidazolin-2-ones from phthalic anhydrides and their antioxidant evaluation

Héctor S. López,[a] José E. Enciso,[a] Adrián Ochoa-Terán,[b] Juan I. Velazquez[c] and Juan I. Sarmiento*[c]

[a] *Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Sinaloa, 80040 Culiacán, Sinaloa, México*
[b] *Centro de Graduados e Investigación en Química, Instituto Tecnológico de Tijuana, 22510 Tijuana, B.C., México*
[c] *Facultad de Ingeniería Culiacán, Universidad Autónoma de Sinaloa, 80040 Culiacán, Sinaloa, México. Fax: +52 667 713 4043; e-mail: jsarmiento@uas.edu.mx*

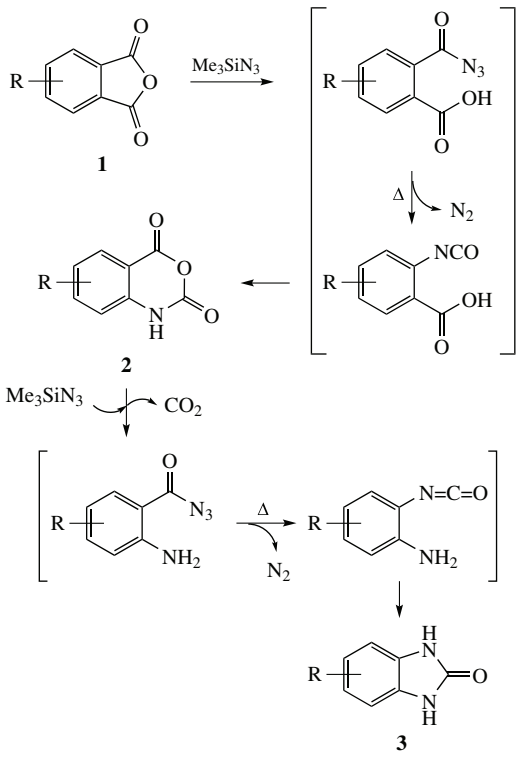
DOI: 10.1016/j.mencom.2016.01.027

Treatment of phthalic anhydride derivatives with trimethylsilyl azide affords benzimidazolin-2-ones in 45–91% yield, which is the result of two consecutive Curtius reactions. Within the series obtained, 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one showed highest antioxidant activity.

Imidazolidinones are commonly synthesized by cyclization of 1,2-diamines with phosgene or 1,1′-carbonyldiimidazole.[1] For the synthesis of imidazolidinones several routes have been reported,[2] but probably the most commonly used methodology involves the use of isocyanates, *i.e.*, the reaction with amino alcohols,[3] amines,[4] α-imino ketones,[5] vinylaziridines[6] and allylamines.[7] Imidazolidinones are found in several natural compounds, *e.g.*, Biotin (vitamin B) which was isolated from yolk, and is a co-enzyme in the carboxylation reaction in the biosynthesis of the fatty acids.[8] Imidazolidinones have been reported against β-secretase (BACE1) inhibitors in Alzheimer's disease,[9] $\alpha_v\beta_3$-antagonist in the prevention and treatment of Osteoporosis,[10] against *Schistosoma mansoni*,[11] selective Human Enterovirus 71 inhibitors,[12] muscarinic M3 selective antagonists.[13] They possess anticancer (A549, COLO205, KATO III, K562),[13(c)] antibacterial and antifungal,[14] and antileishmanial[15] activities.

Recently, we have reported the synthesis of small heterocyclic compounds and their antioxidant evaluation.[16] Currently, our research is focused on the development of a simple one-pot synthesis of small heterocyclic compounds with potential biological activities. In this paper, an easy one-step synthesis of benzimidazolin-2-ones from phthalic anhydride derivatives with trimethylsilyl azide (TMSA) and their antioxidant evaluation are reported.

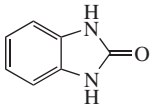
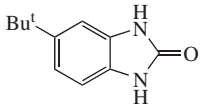
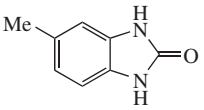
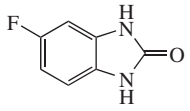
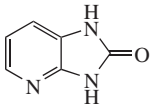
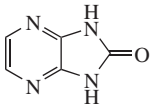
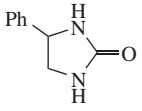
On the treatment of phthalic anhydrides **1** with TMSA the Curtius rearrangement leads to benzoxazine-2,4-dione intermediates **2**, followed by the second Curtius rearrangement and final intramolecular cyclization to provide imidazolin-2-ones **3** (Scheme 1). We started with the optimization of reaction conditions using phthalic anhydride **1a** as a model. First, a comparison between the reaction efficiencies of TMSA generated *in situ* and commercial reagent was made with TLC monitoring until the reaction of the phthalic anhydride was complete. The reactions of TMSA generated *in situ* (from trimethylsilyl chloride with sodium azide) and commercial reagent in THF for 30 h at reflux provided compound **3a** in 20 and 51% isolated yields, respectively. Subsequently, different solvents [DMSO, benzene, acetonitrile and benzene–acetonitrile (3:1 v/v)] were tested under optimal reaction conditions. When DMSO was used as a solvent, product **3a** was not formed and some non-identified by-products were obtained. Probably this reaction follows a mechanism similar to that proposed by Snyder[17] for the synthesis of alkyl chloride from TMSCl. In contrast, the employment of other above solvents



Scheme 1

favored the expected product but gave a lower yield than THF. Note that the matched conditions do not require any sophistication and can be readily accomplished. The solvent was evaporated *in vacuo* and the product precipitated with diethyl ether, to provide the corresponding imidazolin-2-ones in moderate to good yields. The highest yield in THF could be associated with the solubility of reagents and intermediates in this solvent. The yields of imidazolin-2-ones **3a–g** synthesized using this methodology (Table 1)† were 45–91% depending on the structure of the starting material. The structures of the imidazolin-2-ones were confirmed by NMR, IR spectra, and GC-MS. Jones and Schofield[18] reported the synthesis of imidazolin-2-one by a four-step method from 1,2,3,6-tetrahydrophthalic anhydride with TMSA in 72 h to give a 19% of overall yield but obtained a mixture of imidazolin-

Table 1 Yield and antioxidant activity of imidazolin-2-ones obtained.

Entry	Compound	Yield (%)	IC_{50} (μg ml^{-1})
3a		51	2898
3b		52	497
3c		77	660
3d		50	595
3e		91	315
3f		45	384
3g		49	918
	Vitamin C		10.21
	Gallic acid		10.40

2-one and *N*-trimethylsilyloxycarbonyl precursor. Note that *N*-trimethylsilyloxycarbonyl intermediates were not detected in our experiments and only a simple workup procedure was necessary. The synthesis of benzimidazol-2-ones from phthalic anhydride and sodium azide under stronger acid conditions was also described.[19] However, this procedure was hazardous (hydrazoic acid was generated)[20] and not eco-friendly, some by-products were detected and difficult workup was necessary.

† *General procedure*. To a solution of phthalic anhydride in THF (1.0 mM), TMSA (4.0 equiv.) was added and the mixture was refluxed with stirring for 30 h. The resulting solution was concentrated *in vacuo* until a solid formed. The solid was washed with diethyl ether (5×4 ml) to obtain high-purity imidazolin-2-ones **3**.

*1*H-*benz*[d]*imidazol-2(3*H)*-one* **3a**. Yield 51%, mp 364–365 °C, pale brown solid, R_f 0.58 (acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 10.62 (s, 2H), 6.93 (s, 4H). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 155.1, 129.5, 120.3, 108.3. FTIR (ATR, ν/cm^{-1}): 3017, 2898, 2807, 1710, 1629, 1481, 1405, 1361, 1195, 1025. GC-MS, *m*/*z*: 135 [M+H]$^+$.

5-(tert-*Butyl)-1*H-*benz*[d]*imidazol-2(3*H)*-one* **3b**. Yield 52%, mp 312–313 °C, pale brown solid, R_f 0.25 (acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 10.47 (br. s, 2H), 6.98–6.80 (m, 3H), 1.25 (s, 9H), ^{13}C NMR (50 MHz, DMSO-d_6) δ: 155.5, 143.1, 129.5, 127.4, 117.2, 107.9, 105.4, 34.2, 31.6. FTIR (ATR, ν/cm^{-1}): 2956, 1695, 1614, 1475, 1359, 1274, 1027. GC-MS, *m*/*z*: 191 [M+H]$^+$.

*5-Methyl-1*H-*benz*[d]*imidazol-2(3*H)*-one* **3c**. Yield 77%, mp 301–302 °C, pale brown solid, R_f 0.50 (acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 10.47 (d, 2H, *J* 6.6 Hz), 6.81–6.70 (m, 3H), 2.27 (s, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 155.4, 129.8, 129.3, 127.4, 120.9, 109.0, 108.2, 21.0. FTIR (ATR, ν/cm^{-1}): 3100, 2998, 2917, 1677, 1637, 1612, 1506, 1477, 1373, 1209, 1027. GC-MS, *m*/*z*: 149 [M+H]$^+$.

For characteristics of compounds **3d**–**g**, see Online Supplementary Materials.

In a comparative evaluation of antioxidant properties of new molecules gallic acid, ascorbic acid and BHT are commonly used as reference standards.[21] Thus, compounds **3a**–**g** were estimated up to 100 μg ml^{-1} (for details, see Online Supplementary Materials) and exhibited less activity than the reference standards. They revealed an IC_{50} > 100 μg ml^{-1} being inactive as compared with gallic acid (IC_{50} = 10.40 μg ml^{-1}) and vitamin C (IC_{50} = 10.21 μg ml^{-1}). Compound **3e** showed the highest IC_{50} of 315 μg ml^{-1}.

In summary, in this work an easy one-step synthesis of imidazolin-2-ones from phthalic anhydride derivatives and TMSA in good yields has been developed. From a combinatorial chemistry viewpoint, this methodology could allow preparing a mini library of analogues that exhibit the potential of being versatile synthons in the synthesis of wide variety of heterocyclic compounds with expected biological activity.

This work was supported by Consejo Nacional de Ciencia y Tecnología (SEP-CONACyT, grant no. CB-2012-178266-Q).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.01.027.

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Received: 20th May 2015; Com. 15/4630