Ritter reaction of *N*-(hydroxymethyl)saccharin with nitriles: synthesis of new *N*-(amidomethyl)saccharins

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INTRODUCTION

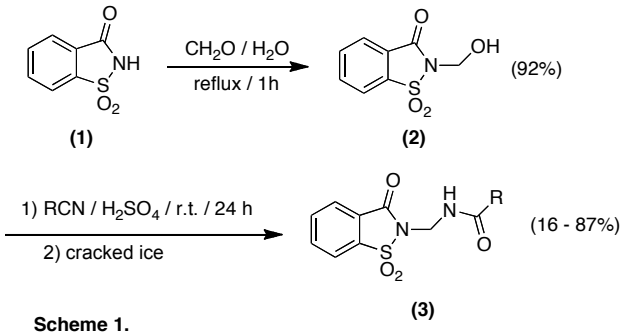
Considerable interest has been focused on saccharin derivatives which have been shown to possess a broad spectrum of biological activities, such as fungicidal, antibacterial, and anti-inflammatory effects.[1,2]

The Ritter reaction, first reported in 1948, allows the formation of amides and it is particularly useful for the preparation of bulky products. In this reaction, a carbocation generated *in situ* from an alcohol, an alcohol derivative, or an olefin is trapped by a nitrile to produce a nitrilium species, which after hydrolysis produces an amide. In the case of alcohols, the substrate itself generates H_2O and the process becomes atom-economical. Other reactions in which a carbocation generated *in situ* is trapped by nitrile are referred to as Ritter-type reactions.[3]

Thus, it was proposed to prepare new drug candidates through the Ritter reaction, by analogy to the work of Buc,[4] condensing *N*-(hydroxymethyl)-saccharin with nitriles.

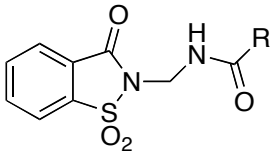
RESULTS AND DISCUSSION

N-(hydroxymethyl)saccharin (**2**), prepared in 92% yield from saccharin (**1**) and formaldehyde,[5] was reacted with equimolar amount of diverse nitriles in H_2SO_4 at room temperature to afford, after work-up, the new crystalline amides (**3**) in 16 – 87% isolated yield. No further purification was necessary, as showed by the analytical data (IR and ^{1}H NMR). (Scheme 1 and Table 1 summarize the results).



Scheme 1.

Table 1. Yields for new *N*-(amidomethyl)saccharins.



(3)

3	R	mp (°C)	Yield (%)*
a	Me	148-150	73
b	Et	> 300	52
c	Ph	159-160	87
d	CH_2=CH	> 300	68
e	CH_2CO_2Et	125-127	16

*Isolated.

CONCLUSION

We have accomplished the synthesis of five new *N*-(amidomethyl)saccharins (**3**) through the Ritter reaction of *N*-(hydroxymethyl)saccharin with nitriles in H_2SO_4.

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