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Facile Synthesis of 3-*N*-Alkyl Pyrimidin-2,4-diones from *N*-Sulfonyloxy Maleimides and Amines

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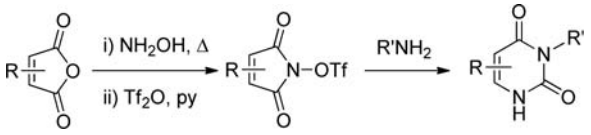
Supporting Information

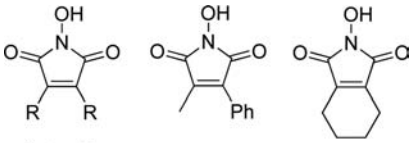
ABSTRACT: Reaction of variously substituted *N*-trifluoromethanesulfonyloxy maleimides with primary amines in the presence of potassium carbonate in DMF at room temperature results in the formation of 3-*N*-alkyl pyrimidin-2,4-diones in good yield.

Nitrogen-based heterocycles are important constituents of a large fraction of approved pharmaceuticals.[1−3] The pyrimidines are second only to the pyridines in occurrence frequency of nitrogen heterocycles in approved drugs.[1−3] The development of new routes to novel classes of substituted pyrimidines is therefore of inherent importance to medicinal chemistry and the drug discovery process. By adapting the limited precedent on the nucleophilic ring opening by hydroxide and borohydride of *N*-toluenesulfonyloxy maleimide and phthalimide derivatives, followed by Lossen rearrangement and either hydrolysis or ring closure,[4,5] we have discovered, and report here, a new method for the synthesis of 3-*N*-alkyl pyrimidin-2,4-diones from maleic anhydrides via reaction of the derived *N*-sulfonyloxy maleimides with amines (Scheme 1).

Scheme 1. Pyrimidindione Synthesis



Brief heating of commercial 2,3-dimethyl and 2,3-diphenyl maleic anhydride with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol[6] gave the corresponding *N*-hydroxy maleimides **1** and **2** in 74% and 80% yield, respectively. Condensation of phenylacetic acid and sodium pyruvate in acetic anhydride afforded 2-methyl-3-phenyl maleic anhydride in 53% yield,[7] which on stirring at room temperature with hydroxylamine hydrochloride and sodium acetate gave *N*-hydroxy-2-methyl-3-phenyl maleimide **3** in 90% yield. The conversion of commercial cyclohexene-1,2-dicarboxylic anhydride to the corresponding *N*-hydroxy maleimide **4**[8] was best achieved by heating with hydroxylamine hydrochloride and sodium acetate to give an intermediate hydroxamic acid. This was followed by cyclization with acetic anhydride to give the *N*-acetoxy imide[5,6] in 25% yield and, finally, deacetylation with benzylamine at room temperature[5] yielding **4** in 62% yield (Supporting Information).



The *N*-hydroxy maleimides **1**−**4** were converted to the corresponding *N*-trifloxy imides **5**−**8** by reaction with triflic anhydride in dichloromethane in the presence of pyridine (Table 1). In the key reaction, stirring of the *N*-trifloxy imides **5**−**8** in DMF at room temperature in the presence of potassium carbonate and a primary amine **9**−**13** smoothly afforded a series of 3-*N*-alkyl pyrimidin-2,4-diones **14**−**27** (Table 1).

The examples presented in Table 1 reveal that the overall process functions with a range of 2,3-disubstituted maleimides including dialkyl (entries 1−3), diaryl (entries 4−6), mixed alkyl, aryl (entries 7−9), and fused bicyclic (entries 10 and 11) systems. The table also illustrates the successful employment of a range of primary amines with varying degrees of steric hindrance and functionality.

Concerning the use of the unsymmetrically substituted *N*-trifloxy 2-methyl-3-phenylmaleimide **7** as an electrophile (Table 1, entries 7−9) two regioisomeric products are formed with a modest preference for the isomer arising from initial nucleophilic attack by the amine on the carbonyl group vicinal to the larger substituent. Presumably this modest preference for nucleophilic attack vicinal to the larger substituent, which is reminiscent of the regioselectivities observed in the nucleophilic ring openings of 2,2-dimethylsuccinic anhydride and 2,2-dimethyl succinimide,[9,10] reflects the greater hindrance to the approach of the nucleophile along the Burgi−Dunitz trajectory in the formation of the minor isomer.

Although not isolated and characterized in each case owing to the formation of regioisomeric and/or diastereomeric mixtures, typical byproducts from these reactions were amido

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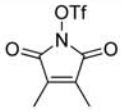
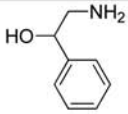
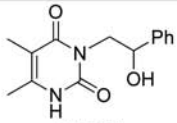
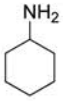
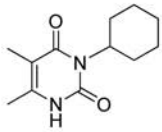
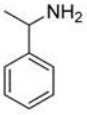
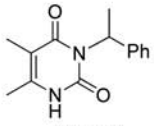
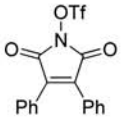
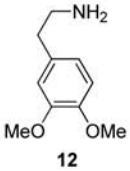
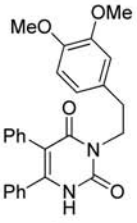
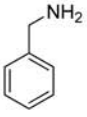
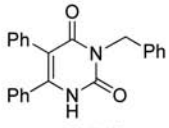
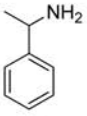
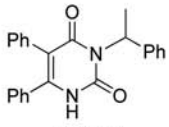
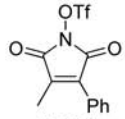
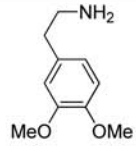
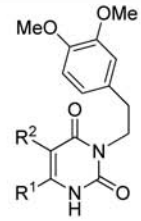
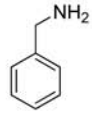
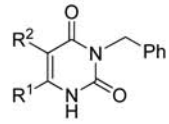
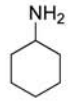
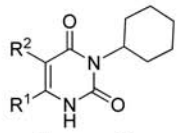
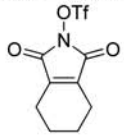
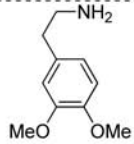
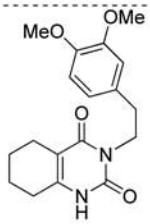
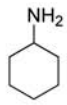
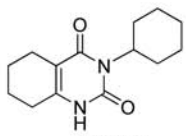
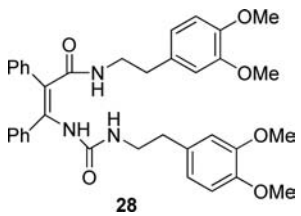
Table 1. Synthesis of *N*-Trifloxy Imides and 3-*N*-Alkylpyrimidin-2,4-diones

entry	*N*-trifloxy imide, % yield	amine	pyrimidindione, % yield
1	 **5**, 77%	 **9**	 **14**, 53%
2		 **10**	 **15**, 56%
3		 **11**	 **16**, 40%
4	 **6**, 89%	 **12**	 **17**, 51%
5		 **13**	 **18**, 54%
6		 **11**	 **19**, 16%
7	 **7**, 67%	 **12**	 **20**: R^1 = Me, R^2 = Ph **21**: R^1 = Ph, R^2 = Me **20** + **21** = 54% **20**:**21** = 1.2:1
8		 **13**	 **22**: R^1 = Me, R^2 = Ph **23**: R^1 = Ph, R^2 = Me **22** + **23** = 51% **22**:**23** = 1.5:1
9		 **10**	 **24**: R^1 = Me, R^2 = Ph **25**: R^1 = Ph, R^2 = Me **24** + **25** = 35% **24**:**25** = 1.5:1
10	 **8**, 57%	 **12**	 **26**, 63%
11		 **10**	 **27**, 55%

ureas. Thus, by way of example, the amido urea **28** was isolated in 7% yield from the preparation of **17** (Table 1, entry 4).



28

Mechanistically, we envisage the formation of the pyrimdindiones to involve nucleophilic ring opening by the amine to give an *O*-triflated amido hydroxamic acid derivative that undergoes rapid Lossen rearrangement[11−13] to afford an amido isocyanate. Finally, nucleophilic attack of the amide on the isocyanate yields the products. External attack by a further equivalent of amine on the amido isocyanate affords the byproduct amido ureas (Scheme 2).

Precedent for this mechanism derives from the work of Hurd and co-workers who studied the decomposition of the disodium salt of *O*,*O*′-dibenzoyl phthalohydroxamic acid in water at reflux. The observed formation of 3-*N*-benzoyloxy quinazolinedione in 37% yield was considered to involve Lossen rearrangement of a single of the two activated hydroxamate derivatives to give an isocyanate that was subsequently trapped intramoleculary by nucleophilic attack of the second hydroxamate salt.[14] Lossen rearrangement of sodium succinohydroxamate on reaction with benzenesulfonyl

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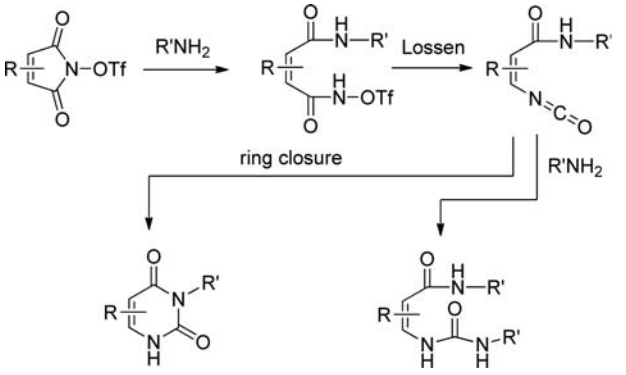
Scheme 2. Reaction Mechanism



chloride is likewise known to afford 3-*N*-benzenesulfonyloxy dihydrouracil.[15] Thermal Lossen rearrangement and subsequent ring closure of mono- and dihydroxamic acid derivatives of pyridine-1,2-dicarboxylic acid also has been reported.[16] Nucleophilic ring opening of *N*-toluenesulfonyloxy maleimide and phthalimide by either hydroxide or borohydride followed by Lossen rearrangement of the intermediate *N*-sulfonyloxyhydroxamic acid derivative has also been described.[4,5] In the maleimide series with hydroxide as a nucleophile, after the Lossen rearrangement a series of hydrolysis steps gives a β-keto-acid and eventually a simple ketone devoid of both of the original carboxyl cations.[4] In the phthalimide series, with borohydride as the nucleophile, the initially formed alcohol cyclizes onto the isocyanate generated in the Lossen rearrangement to give a cyclic urethane.[5]

In so far as the *N*-hydroxy maleimides are assembled directed from the corresponding maleic anhydrides,[18] for which a variety of facile synthetic methods are available, this novel pyrimidindione synthesis complements and extends the existing uses of cyclic anhydrides[19] and thioanhydrides[20−23] in formal multicomponent processes. This novel synthesis of pyrimidindiones also complements existing methods for the synthesis of this class of heterocycles[24] and the use of the Biginelli multicomponent synthesis of dihydropyrimidines,[25,26] and other multicomponent approaches to pyrimidines themselves.[27]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02079.

Full experimental details and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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