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Intramolecular Electrophilic Aromatic Substitution Reactions of 2-Amidoacroleins: A New Method for the Preparation of Tetrahydroisoquinolines, Tetrahydro-3-benzazepines, and Hexahydro-3-benzazocines

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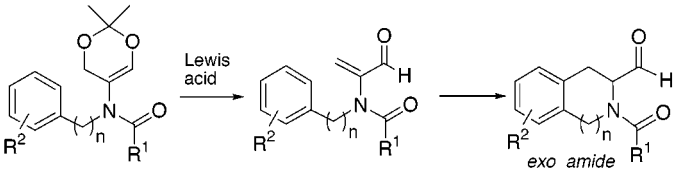
ABSTRACT



A variety of heterocyclic ring systems can be prepared by subjecting *N*-aryl-substituted 5-amido-1,3-dioxins to Lewis acids. The reactions proceed via catalyzed retrocycloadditions to afford 2-amidoacroleins and concomitant regioselective electrophilic aromatic substitution reactions. The transformation is also successful using dioxins with amides that are within the incipient ring to afford the analogous lactams.

The β-phenethylamine pharmacophore is present in numerous biologically active compounds either in its acyclic form or embodied in polycyclic frameworks.[1] The diverse biological properties of these compounds has stimulated the development of extensive methodology for their preparation. We envisaged a conceptually new approach to these compounds based upon our recently reported synthesis of 2-amidoacroleins via retrocycloaddition reactions of 5-amido-1,3-dioxins.[2] We had previously employed these reactants as dienophiles or heterodienes in natural product synthesis endeavors and have continued to exploit their excellent reactivity properties in reactions other than cycloadditions. In the case at hand (Scheme 1), it was hoped that Lewis acid activated amidoacroleins **2** and **5**, generated from the corresponding dioxins **1** and **4**, respectively, might serve as the electrophilic components in a variety of intramolecular electrophilic aromatic substitution reactions.[3,4] The products that emerge from this transformation, amides **3** and lactams **6**, both contain the desired β-phenethylamine substructure but differ by the location of the amide carbonyl, versatility that is of value for strategic bond construction(s) in projected total synthesis applications. Herein we report on the scope and limitations of this new methodology and document its usefulness in the preparation of novel morphine analogues.

The various protocols that have been developed for the preparation of the requisite 5-amido-1,3-dioxins are shown in Scheme 2. Treatment of 1,3-dioxin-5-one[5] (**7**) with primary amines in the presence of 4 Å molecular sieves afforded the corresponding imines **8**. This condensation proceeds at a faster rate in chloroform, although it is more convenient to

(1) (a) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148 and previous reviews therein. (b) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck & Co., Inc.: Whitehouse Station, NJ, 1996.

(2) (a) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2000**, *3*, 1125. (b) Funk, R. L.; Greshock, T. J., submitted for publication.

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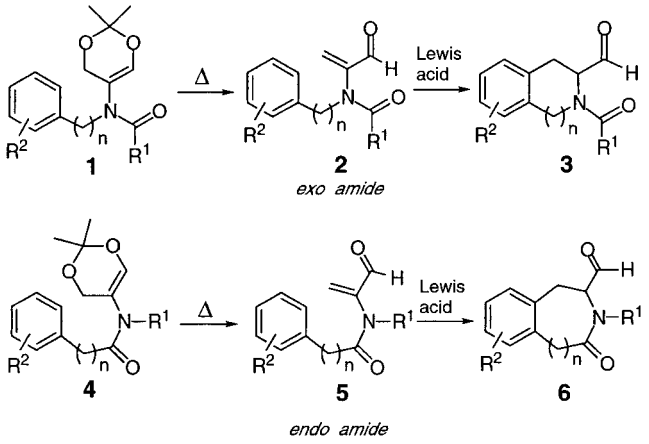
Scheme 1



use toluene since it is the preferred solvent for the subsequent enamide formation. Thus, either anhydrides and diisopropylethylamine (Table 1, entries 1, 2, and 3) or acid chlorides and lutidine (entries 4, 8, and 9) are added to the toluene solution of imines to afford the desired 5-amido-1,3-dioxins in good yields. 5-Triflamido-1,3-dioxins **10** can also be prepared by addition of triflic anhyride and diisopropylethylamine to the corresponding imine (Table 1, entry 6). When the *N*-(*m*-methoxyphenethyl)imine **8** was subjected to these conditions, none of the desired dioxin (cf. entry 5) was isolated. Instead, a product derived from a competitive Pictet−Spengler cyclization of the presumed trifluoromethylsulfonyl iminium ion intermediate was obtained. Accordingly, the *N*-benzyl triflamide **10** (R^1 = Bn) was hydrogenated with Pearlman's catalyst to afford triflamide **11**, which in turn could be smoothly alkylated[6] with alkyl halides to establish an alternative route to 5-triflamido-1,3-dioxins **10** (entries 5 and 7).

We were pleased to discover that the 5-amido-1,3-dioxins shown in Table 1 underwent facile Lewis acid catalyzed retrocycloadditions to 2-amidoacroleins and concomitant, albeit slower, regioselective cyclization to a variety of heterocyclic ring systems. These cyclizations are especially

Scheme 2

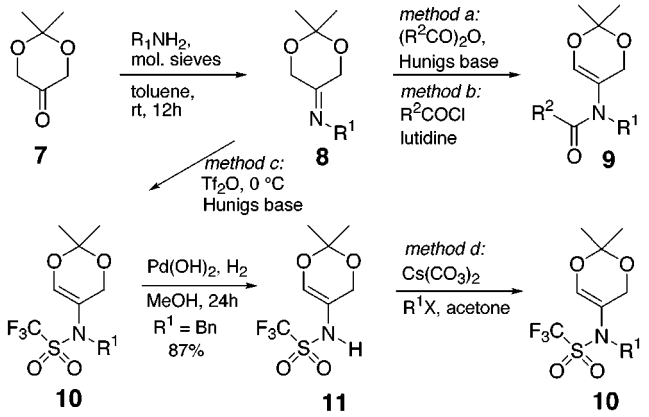
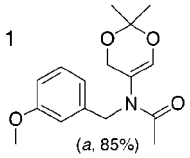
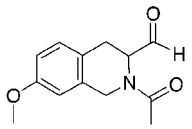
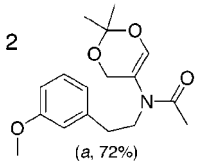
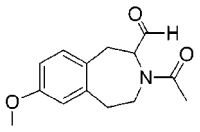
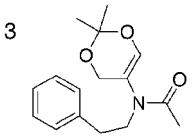
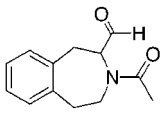
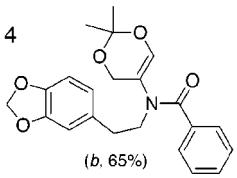
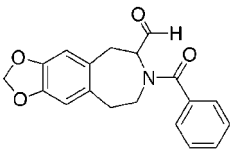
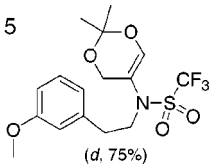
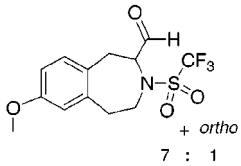
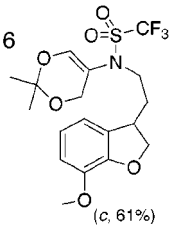
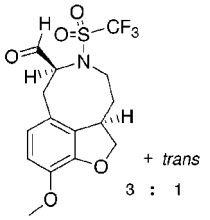
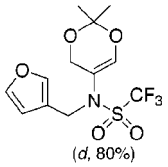
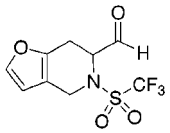
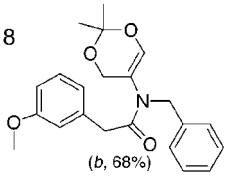
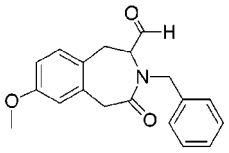
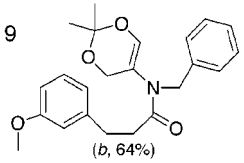
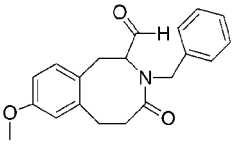


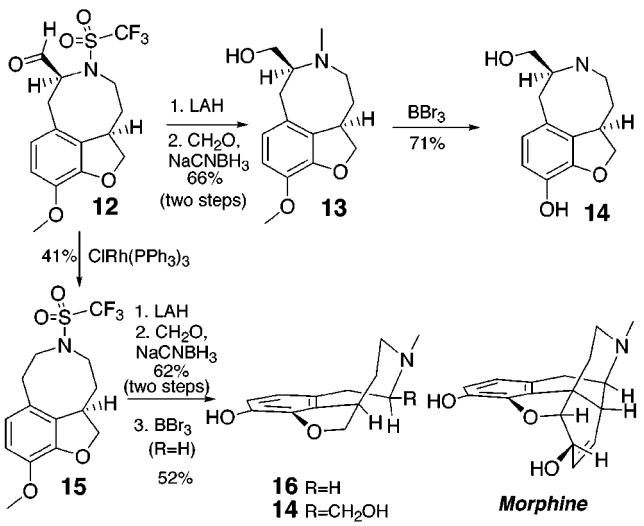
Table 1. Intramolecular Electrophilic Aromatic Substitution Reactions of 2-Amidoacroleins Generated in Situ from 5-Amido-1,3-dioxins

entry	5-amido-1,3-dioxin (method, yield)	conditions (yield)	product
1	 (*a*, 85%)	$CHCl_3$, rt, 2h; 2 equiv $BF_3{\cdot}OEt_2$ (61%)	
2	 (*a*, 72%)	$CHCl_3$, rt, 1h; 2 equiv $BF_3{\cdot}OEt_2$ (67%)	
3	 (*a*, 65%)	$MeNO_2$, rt, 12h; 2 equiv $AlCl_3$ (67%)	
4	 (*b*, 65%)	$CHCl_3$, 55 °C, 2h; 2 equiv $BF_3{\cdot}OEt_2$ (61%)	
5	 (*d*, 75%)	$CHCl_3$, rt, 0.75h; 0.1 equiv $SnCl_4$ (68%)	 + *ortho* 7 : 1
6	 (*c*, 61%)	$CHCl_3$, 50 °C, 8h; 0.1 equiv $SnCl_4$ (71%)	 + *trans* 3 : 1
7	 (*d*, 80%)	$CHCl_3$, rt, 8h; 0.1 equiv $SnCl_4$ (75%)	
8	 (*b*, 68%)	$CHCl_3$, rt, 1h; 2 equiv $BF_3{\cdot}OEt_2$ (61%)	
9	 (*b*, 64%)	$CHCl_3$, rt, 12h; 2 equiv $BF_3{\cdot}OEt_2$ (54%)	

noteworthy considering that none of the previously reported examples of intramolecular electrophilic aromatic substitution reactions employ unsaturated aldehydes as the electrophile[3] and only one cyclization of an unsaturated carbonyl compound that lacked carbocation stabilizing groups on the β-carbon (a 7-*endo* ketone) has been reported.[3h] Thus, as we had planned, the amide moiety may be *exo* to the incipient ring (entries 1−7) or *endo* to afford lactams (entries 8 and 9). To date, a tetrahydroisoquinoline (entry 1), as well as 3-benzazepines (entries 2−5 and 8) and 3-benzazocines (entries 6 and 9) have been prepared using this method. The reaction times indicate that a seven-membered ring closure is preferred over the six- and eight-membered counterparts (entry 2 vs. entry 1 and entry 8 vs. entry 9) in keeping with molecular modeling that suggests a more accessible Wheland intermediate for a seven-membered closure. Not surprisingly, the cyclizations with the more electron-withdrawing triflamidoacroleins are more facile than the acetamido or benzamido variants and, consequently, can be catalyzed with a milder Lewis acid ($SnCl_4$) in substoichiometric quantities (entry 5 vs. entries 2 and 4). Moreover, activated aromatic rings are not essential for successful cyclization, although more forcing conditions are required (entry 3 vs. entry 2). Finally, the example shown in entry 7 demonstrates that aromatic ring systems other than substituted benzenes participate in this type of cyclization en route to uncommon heterocyclic ring systems.

To demonstrate that this methodology is indeed capable of providing compounds possessing β-phenethylamine pharmacophores, the product of entry 6, benzazocine **12** (Scheme 3), was converted to the new morphine analogues **14** and **16**.[7] To that end, simultaneous reduction of the aldehyde

Scheme 3



moiety and removal of the triflamide group[6] was accomplished by treatment of benzazocine **12** with lithium aluminum hydride. The resulting secondary amine was methylated using the standard reductive amination protocol, and the methyl ether of the product **13** was cleaved with boron tribromide to provide morphine analogue **14**. Morphine analogue **16** was obtained by initial decarbonylation of benzazocine **12** using the Wilkinson reagent in refluxing xylene to afford the triflamide **15**, which was then subjected to the same three-step sequence used to prepare analogue **14**.[8]

In summary, we have shown that intramolecular aromatic substitution reactions of amidoacroleins constitute a new strategy for preparing heterocyclic compounds that embody the biologically significant β-phenethylamine substructure. The three-component aspect of this methodology, i.e., 1,3-dioxin-5-one, primary amine, and acylating/sulfonylating agent, makes it readily adaptable to natural product total synthesis endeavors. Several possibilities are under consideration and will be reported in due course.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (GM28553).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016592N

(3) For selected examples of Lewis acid mediated intramolecular electrophilic aromatic substitution reactions using unsaturated carbonyl compounds, see: *endo carbonyl* (a) Smith, L. I.; Prichard, W. W. *J. Am. Chem. Soc.* **1940**, *62*, 778. (b) Colonge, J.; Chambard, R. *Bull. Soc. Chem. Fr.* **1953**, 982. (c) Parham, W. E.; Wheeler, E. L.; Dodson, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 1166. (d) Pandey, R. C.; Dev, S. *Tetrahedron* **1968**, *24*, 3829. (e) Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, R. L.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. J. *J. Med. Chem.* **1984**, *27*, 1516. (f) Janusz, J. M.; Young, P. A.; Scherz, M. W.; Enzweiler, K.; Wu, L. I.; Gan, L.; Pikul, S.; McDow-Dunham, K. L.; Johnson, C. R.; Senanayake, C. B.; Kellstein, D. E.; Green. S. A.; Tulich, J. L.; Rosario-Jansen, T.; Magrisso, I. J.; Wehmeyer, K. R.; Kuhlenbeck, D. L.; Eichold, T. H.; Dobson, R. L. M. *J. Med. Chem.* **1998**, *41*, 1124. (g) Bergman, J.; Venemalm, L.; Gogoll, A. *Tetrahedron* **1990**, *46*, 6067. (h) Nagao, Y.; Lee, W. S.; Komaki, Y.; Sano, S.; Shiro, M. *Chem. Lett.* **1994**, 597. (i) Ho, T.-L.; Yang, P.-F. *Tetrahedron* **1995**, *51*, 181. *exo carbonyl* (j) Stork, G.; Burgstahler, A. *J. Am. Chem. Soc.* **1951**, *73*, 3544. (k) Murphy, W. S.; Watanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1555. (l) Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. (m) Kashihara, H.; Shinoki, H.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1986**, *11*, 4527. (n) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555.

(4) For the photocyclization of a 2-(benzamido)acrylates, see: (a) Schultz, A. G.; Sha, C.-K. *Tetrahedron* **1980**, *36*, 1757. (b) Naito, T.; Ninomiya, I. *Heterocycles* **1988**, *27*, 1325. (c) Pyne, S. G.; Schafer, K. *Tetrahedron* **1998**, *54*, 5709. For the intramolecular Heck reactions of 2-{*N*-[(iodoaryl)alkyl]-*N*-(*tert*-butoxycarbonyl)-amino}acrylates, see: (d) Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447.

(5) Prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride. Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, 45, 687.

(6) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517. (b) Hendrickson, J. B.; Bair, K. W.; Bergeron, R.; Giga, A.; Skipper, P. L.; Sternbach, D. D.; Wareing, J. A. *Org. Prep. Proced. Int.* **1977**, *9*, 173.

(7) 3-Benzazocine analogues of morphine similar to **16** but lacking the dihydrofuran ring have been previously reported; see: (a) Pecherer, B.; Stumpf, J.; Brossi, A. *Helv. Chim. Acta* **1970**, *53*, 763. (b) Hori, M.; Kataoka, T.; Shimizu, H.; Imai, E.; Koide, T.; Iwata, N.; Kurono, M. *Chem. Pharm. Bull.* **1990**, *38*, 8. (c) Lai, B.; Bhedi, D. N.; Gidwani, R. M.; Sankar, C. *Tetrahedron* **1994**, *50*, 9167 and ref 1 therein. Moreover, molecular mechanics calculations suggest that the dihydrofuran ring as well as the hydroxymethyl substituent of **14** contribute to the significant population of the morphine-like conformer shown (0.75 kcal/mol above global minimum, 8% of a Boltzmann distribution of all conformers at 300 °K).

(8) Benzazocines **14** and **16** have been submitted for biological evaluation. These studies will be reported separately.