Combinatorial Chemistry

DOI: 10.1002/anie.200501665

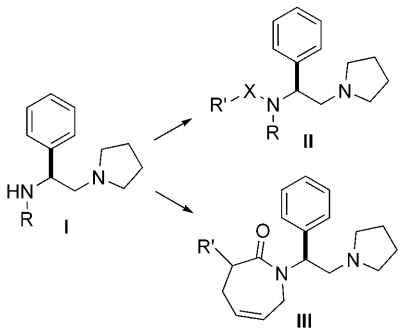
Solid/Solution-Phase Annulation Reagents: Single-Step Synthesis of Cyclic Amine Derivatives

Roland E. Dolle, Calum MacLeod, Blanca Martinez-Teipel, William Barker, Pamela R. Seida, and Torsten Herbertz*

Single-step amine-derivatization chemistry is one of the most powerful and practical streamlined synthetic techniques available to the medicinal and combinatorial chemist. Acylation, sulfonylation, ureidoation, heteroarylation, reductive amination, and alkylation are used extensively to create libraries of amine derivatives.[1] Researchers involved in drug discovery particularly appreciate the importance of such high-throughput chemistries used to create nascent structure–activity relationships (SARs) and to expand the intellectual property field around a novel biologically active lead. Amine derivatization is conveniently carried out in the solution phase with a scavenger resin(s) to assist in the removal of the excess derivatizing reagent and/or product purification.[2] Activated resins have also been developed in which an amine is treated with a resin-bound functional-group-transfer reagent suspended in a suitable solvent.[3a] Following filtration, which removes both the spent and excess reagent, and solvent evaporation, derivatives are generally produced in over 75% purity, which is suitable for biological screening. Examples of this type of reagent are the commercially available carboxyl- and sulfonyl-activated tetrafluorophenol (TFP) resins developed by Salvino et al. for amide and sulfonamide synthesis.[3b]

During the course of a drug-discovery program directed toward the identification of peripherally restricted κ-opioid receptor agonists, we conducted a high-throughput *N*-derivatization campaign for diamine **I**, including the use of TFP resins, to define the SAR in this region of the pharmacophore (**I**→**II**; X = CO, SO_2, HNCO; Scheme 1). In related SAR studies, conformationally restricted analogues **III** were prepared by ring-closing metathesis as the method for the generation of the azepinone ring.[4] In contrast to the hours of labor required to generate acyclic analogues **II** by semi-automated parallel synthesis, the synthesis of cyclic analogues **III** required a multistep sequence and several months of labor. Access to robust reagents to carry out single-step amine annulations would have accelerated the synthesis and biological evaluation of **III** and related heterocyclic analogues. However, there are no generally recognized "off-the-shelf"

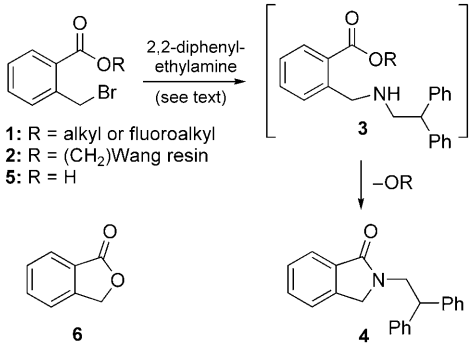
[*] Dr. R. E. Dolle, Dr. C. MacLeod, Dr. B. Martinez-Teipel, W. Barker, Dr. P. R. Seida, Dr. T. Herbertz
Department of Chemistry
Adolor Corporation
700 Pennsylvania Drive, Exton, PA 19341 (USA)
Fax: (+1) 484-595-1551
E-mail: rdolle@adolor.com



Scheme 1. Amine derivatization leading to κ-opioid receptor agonists.[4]

reagents for high-throughput amine annulation. An exploratory chemical-technology program was initiated to address this gap in methodology, and so develop reagents for rapid amine annulation. Approaches were sought to produce monocyclic, bicyclic, spirocyclic, and polycyclic ring systems from primary amines in one step that would be amenable to semiautomated library production in a manner analogous to the acyclic derivatization protocols. The acronym SPAn, derived from solid/solution-phase annulation, collectively refers to the technology, reagents, and products thereof. The first examples of this conceptually new family of SPAn reagents, which yield five-, six-, and seven-membered heterocycles from primary amines, are introduced.

A tandem *N*-alkylation/intramolecular acylation reaction that yields an isoindolinone was selected as the prototypical annulation reaction to be investigated (**1/2**→**3**→**4**; Scheme 2).[5] The results of the initial solution-phase experi-



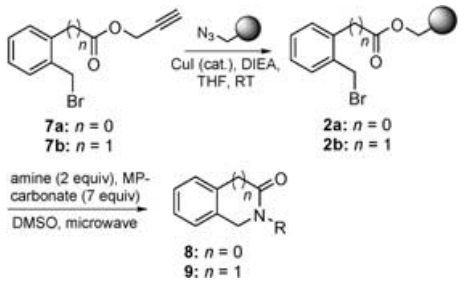
Scheme 2. Annulation strategy for isoindolinone **4**.

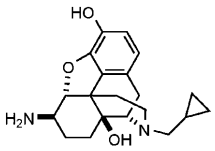
ments with assorted esters **1** and 2,2-diphenylethylamine in a range of solvents under both thermal and microwave reaction conditions were unsatisfactory. As a result, our attention turned to the employment of a cyclorelease strategy[6] and the preparation of resin-bound reagent **2**. The dilemma that immediately surfaced with this approach was the efficient loading of acid **5**. Direct coupling of **5** to Wang resin by employing a range of coupling reagents and reaction conditions resulted in capricious loading, even when **5** was used in large excess. Substantial amounts of lactone **6** formed, which is a testament to the reactivity and instability of this material. In light of this experience and the potential for the troublesome loading of other reactive esters of interest, an alternative method for the generation of the resin-bound reagent was required. The copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes is a robust ligation method that occurs under very mild reaction conditions.[7] Gmeiner and co-workers recently employed this approach to create new amide-backbone[8a,b] and acrylate-based (REM) linkers[8c] for solid-phase organic synthesis. With this methodology in mind, bromide **7a** (5 equiv; prepared from 2-bromomethylbenzoic acid (1 equiv), propargyl alcohol (3 equiv), *N*,*N*′-diisopropylcarbodiimide (1.2 equiv), and dimethylaminopyridine (cat.) in 48% yield) was added to a suspension of Merrifield azide resin[8a] in dichloromethane followed by the addition of excess diisopropylethylamine (DIEA) and 0.02 equivalents of CuI. The reaction was monitored by single-bead FTIR (disappearance of absorption at 2096 cm^{-1}), and resin **2a** was obtained in good yield (65% as determined by elemental analysis) after 20 hours on an orbital shaker. Importantly, the loading was reproducible (5 runs, 65–70% yield). Subsequent reaction of **2a** with 2,2-diphenylethylamine (2 equiv) in dimethyl sulfoxide (DMSO) with excess MP-carbonate (7 equiv; Polymere Labs) under microwave conditions (150°C for 15 min following a 30-min temperature ramp-up from 25 to 150°C) afforded the desired annulated product **4** in 90% crude purity (UV: $\lambda 1 = 220$ nm; $\lambda 2 = 254$ nm) and 33% yield of the isolated product. It was subsequently found that both the chloro and iodo ester analogues of **2** also load efficiently, but only the iodo resin gave equivalent or higher yields and purity of **4**. For this reason, bromide and iodide were the preferred halogen leaving groups in the SPAn reagents. Unlike **1**, which spontaneously decomposed to **6** and other unidentified materials, the resin-bound reagent **2a** was stable for months when stored at ambient temperature and humidity.

Given the success of this first annulation reaction, the chemistry was expanded to include homologue **2b** and the preparation of a 20-member library of isoindolinones **8** and isoquinolones **9** (Table 1). A range of primary amine substrates was successfully annulated in a single step, including substituted alkyl- **A1**, **A4**; alkylaryl- **A2**, **A9**; heteroarylalkyl- **A3**, **A6–8**; and heterocycloalkylamines **A5** and the sterically demanding 6β-naltrexamine (**A10**). An average yield of 30% and a purity of greater than 90% was obtained following chromatographic purification.

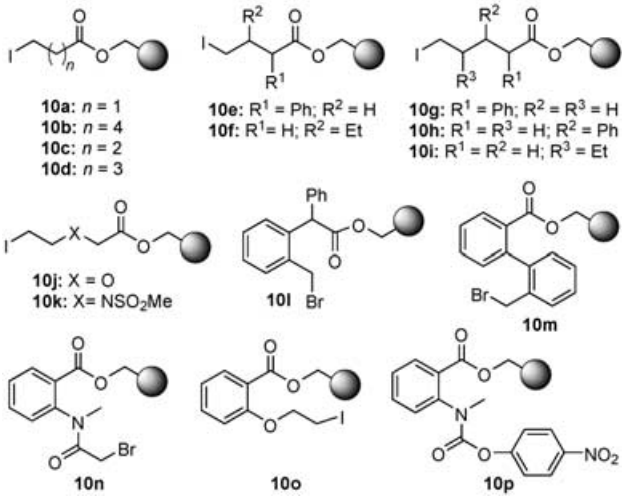
To explore the scope of the SPAn chemistry in terms of ring sizes that may be obtained, iodo esters **10a–d** were synthesized (Scheme 3). Reaction of the resins with a representative amine, phenoxyethylamine (**A1**), under the reaction conditions defined above afforded pyrrolidinone (**11c**; 29%) and piperidinone (**11d**; 24%; Scheme 4). Azetidinone (**11a**) and azepinone (**11b**) were not detected in the crude reaction mixtures. Seven-membered-ring annulation products were obtained, however, provided that a conformational constraint biased the system toward cyclization. For example, reagents **10m–o**, in which the acyl and haloalkyl groups are *ortho*-disposed on an aromatic ring, furnished **11m**, **11n**, and **11o** (21, 23, and 12%, respectively) upon annulation of **A1**.

Table 1: Isoindolinone **8** and isoquinolone **9** library from SPAn reagents **2a**,**b**.



Amine		SPAn reagent	Annulation product	Yield [%][a]
2-phenoxyethylamine	**A1**	**2a**	**8a**	32
		2b	**9a**	32
2-(4-chlorophenyl)ethylamine	**A2**	**2a**	**8b**	29
		2b	**9b**	30
(pyridin-3-yl)methylamine	**A3**	**2a**	**8c**	24
		2b	**9c**	32
2-(*N*-morpholino)ethylamine	**A4**	**2a**	**8d**	24
		2b	**9d**	36
4-amino-(*N*-Boc-piperidine)	**A5**	**2a**	**8e**	42
		2b	**9e**	30
(thiophen-2-yl)methylamine	**A6**	**2a**	**8f**	61
		2b	**9f**	26
(5-methylfuran-2-yl)methylamine	**A7**	**2a**	**8g**	40
		2b	**9g**	25
(5-methylisoxazol-3-yl)-methylamine	**A8**	**2a**	**8h**	21
		2b	**9h**	22
(*S*)-methylbenzylamine	**A9**	**2a**	**8i**	45
		2b	**9i**	31
	**A10**	**2a**	**8j**	33
		2b	**9j**	17

[a] Yield of isolated product, as purified by HPLC.



Scheme 3. Additional selected examples of SPAn reagents.

The introduction of substituents into these reagents adds elements of stereochemical and shape diversity in the annulation products. SPAn reagents **10e–i** with pendent aryl (phenyl) or alkyl (ethyl) groups furnishes substituted pyrrolidinones **11e,f** and piperidinones **11g–i** (**A1**; 23–62% yield). This result is significant for two reasons: First, the chemical reactivity of the SPAn reagents was expanded to include displacement of less-reactive nonbenzylic halogen centers in the tandem alkylation/intracyclization process. Second, the unique three-dimensional disposition of the ring functionalities present in **11e–i** permits a thorough interrogation of biological space. The differential display of the chemical functionalities by the annulation products is ideal for the development of a SAR against a given molecular target. These results are analogous, albeit accentuated by the conformational rigidity of the cyclic derivatives, to SAR information that may be obtained when traditional acyclic derivatization is performed. The swath of chemical space occupied by the SPAn products is assessed visually by examination of the overall topography of all of the annulation products listed in Scheme 4 (Figure 1a). The importance of shape sampling in relation to biological activity is illustrated in the derivatization of 6β-naltrexamine (**A10**) with reagents **2a**,**b**. The α-phenylpyrrolidinone derivative **8j** exhibits a K_i value of 1.6 nM against the μ-opioid receptor, whereas $K_i =$

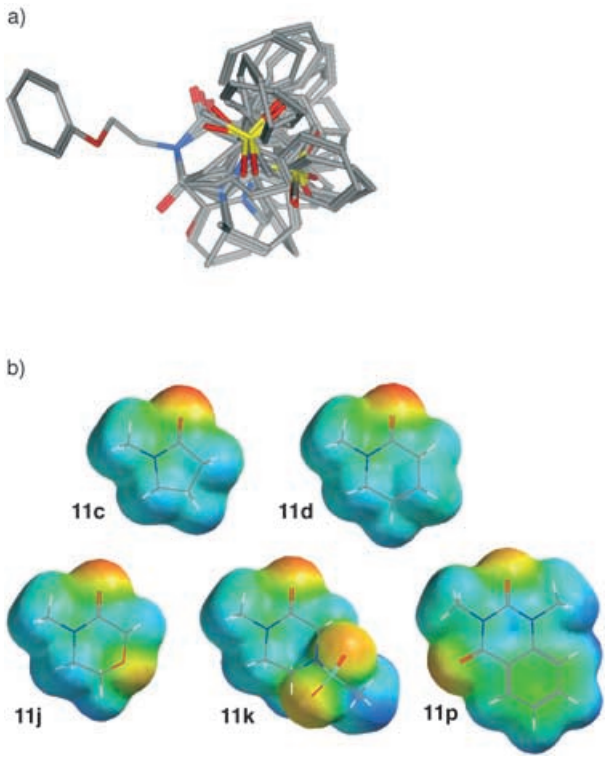
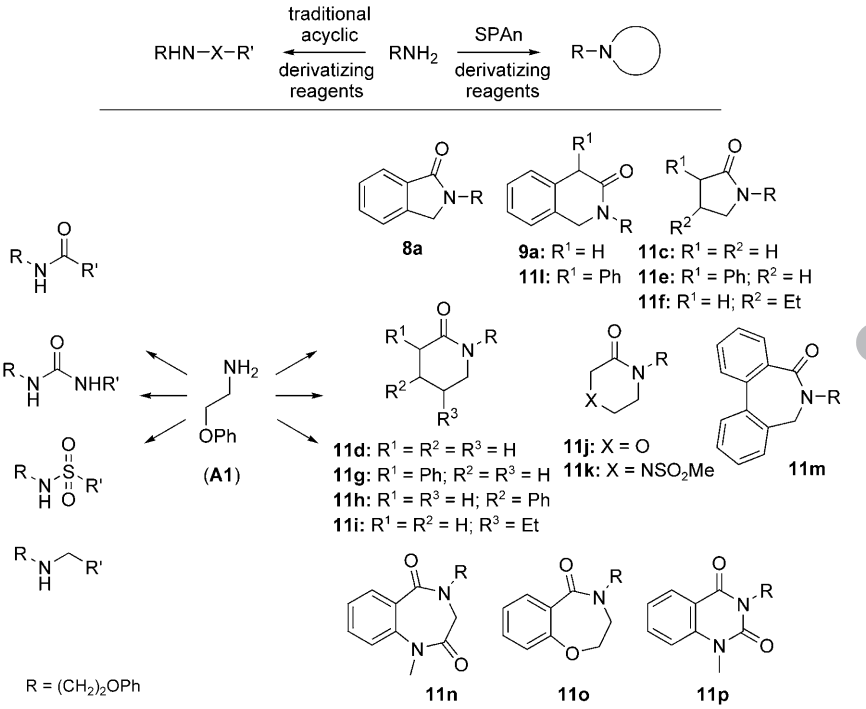


Figure 1. a) The collective topology of SPAn products given in Scheme 4 indicates dense interrogation of chemical space. The phenoxyamide linkage was kept fixed and low-energy conformations of the side chains of **11c–p** were calculated by using the MMFF94x forcefield in the molecular operating environment (MOE; Chemical Computing Group). The structures were aligned with respect to the atoms making up the phenoxyamide linker. b) Graphical comparison of electrostatic potential surfaces of **11c**,**d** versus **11j**,**k**,**p**, as derived from HF/3-21g* calculations by using Spartan '04. The electrostatic potential values range from −67 (red) to 37 kcal mol^{-1} (blue). The phenoxyethyl group is replaced with a methyl group for clarity.



Scheme 4. Use of SPAn reagents for cyclic amine derivatization.

56 nM for the α-phenylpiperidinone derivative **9j** at this receptor. The increase in ring size by a single methylene unit causes a remarkable 35-fold decrease in binding affinity.

Replacement of the methylene carbon atoms in **10b**,**c** by a heteroatom generates reagents **10j**,**k** which afford morpholinone **11j** (**A1**; 29%) and piperazinone **11k** (**A1**; 21%). These cyclic and related heteroatom-containing derivatives **11n–p**, give rise to electrostatic potential (EP) surfaces, distinct from their carbon congeners.[9] This result is again evident upon visual inspection of the EP surfaces generated for **11j**,**k**,**p** and carbon congeners **11c**,**d** (Figure 1b). The complementarity of the EP surface and molecular shape are two mutually inclusive determinants for high-affinity binding. Both of these molecular attributes are readily probed by employing the annulation chemistry.

A new family of reagents for amine derivatization, termed SPAn reagents, enables the single-step conversion of primary amines to cyclic derivatives. The annulation protocol, together with existing protocols for the preparation of amides, sulfonamides, ureas, and other acyclic derivatives in one step (Scheme 4), represents a powerful ensemble for streamlined synthesis. Resin loading, a major obstacle in reagent preparation, was overcome through the 1,3-dipolar cycloaddition reaction of solution-prepared propargyl esters and Merrifield azide resin. The reagents require no further chemical manipulation or activation for their use and display excellent shelf stability. Microwave heating was essential to obtain the annulation products as discrete compounds **11c–p** or in a library format (**2a**,**b**→**8/9a–j**, respectively). Tandem *N*-alkylation/intramolecular acylation is utilized in this report as the annulation manifold to yield heterocyclic lactams. Reagents that afford cycloalkylamines, diazaspirocycles, and other non-lactams have also been developed by us, thus increasing the molecular diversity of the cyclic derivatives obtained. Application of SPAn chemistry in the context of finding new lead compounds and SAR development will be reported subsequently.[10]

Received: May 13, 2005
Published online: August 3, 2005

Keywords: amines · annulation · combinatorial chemistry · cycloaddition · heterocycles

[1] R. E. Dolle, *J. Comb. Chem.* **2003**, *6*, 623–679, and references therein.
[2] S. Bhattacharyya, *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 752–764.
[3] a) J. M. Salvino, R. E. Dolle in *Methods in Enzymology*, *Vol. 369*, *Part B* (Eds.: G. A. Morales, B. A. Bunin), Elsevier Academic Press, Amsterdam, **2003**, pp. 151–163; b) J. M. Salvino, N. V. Kumar, E. Orton, J. Airey, T. Kiesow, K. Crawford, R. Mathew, P. Krolikowski, M. Drew, D. Engers, D. Krolinkowski, T. Herpin, M. Gardyan, G. McGeehan, R. Labaudiniere, *J. Comb. Chem.* **2000**, *2*, 691–697.
[4] P. A. Tuthill, P. R. Seida, W. Barker, J. A. Cassel, S. Belanger, R. N. DeHaven, M. Koblish, S. L. Gottshall, P. J. Little, D. L. DeHaven-Hudkins, R. E. Dolle, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5693–5697.
[5] V. A. Kovtunenko, A. K. Tyltin, T. T. Dobrenko, F. S. Babichev, *Ukr. Khim. Zh.* **1983**, *49*, 1099–1103.
[6] J. H. van Maarseveen, *Comb. Chem. High Throughput Screening* **1998**, *1*, 185–214.
[7] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
[8] a) S. Lober, P. Rodriguez-Loaiza, P. Gmeiner, *Org. Lett.* **2003**, *5*, 1753–1755; b) L. Bettinetti, S. Lober, H. Huebner, P. Gmeiner, *J. Comb. Chem.* **2005**, *7*, 309–316; c) S. Lober, P. Gmeiner, *Tetrahedron* **2004**, *60*, 8699–8702.
[9] J. S. Murray, P. Politzer, *Methods Princ. Med. Chem.* **2003**, *17*, 233–254.
[10] The authors wish to acknowledge P. C. Kambhampati, D. Subrahmanyam, V. S. Ponnapalli, L. M. Kolukuluri, Y. Deraje, and M. R. Motatipally, of GVK Biosciences PVT, Ltd., Hyderabad, India, for their assistance in the preparation of propargyl esters, the details of which will be reported separately.

