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Parallel solution phase synthesis of *N*-substituted 2-pyrazoline libraries

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Abstract

The value of α,β-unsaturated ketones (chalcones) as templates for the combinatorial assembly of *N*-substituted 2-pyrazolines has been explored. Based on a set of 80 chalcones, an array of 1500 *N*-carbamoyl, carbonyl and sulfonyl pyrazolines were produced demonstrating that a broad range of diversity can be fabricated around the pyrazoline motif. The efficient utilization of polymer-supported reagents and scavengers aided in providing typical purities of 75–98%. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: pyrazolines; chalcones; polymer-supported reagents/scavengers; combinatorial chemistry.

During the last few years, the utilization of combinatorial chemistry as a pharmaceutical drug discovery tool has rapidly evolved.[1] Initial demonstrations of its use focused on the solid phase synthesis of compound libraries, whereas more recently, solution phase chemistry for library generation has been receiving increased attention.[2] Advances in liquid/liquid extraction,[3] solid phase extraction,[4] polymer-bound reagents[5] and scavengers[6] now allow for multi-step solution phase parallel syntheses in excellent purities without the need of traditional chromatographic techniques.[7]

Our interest in the development of practical processes for creating 'diverse drug-like' chemical libraries via automation, led us to explore the concept of using α,β-unsaturated ketones (chalcones) as key intermediates for combinatorial manipulation. Studies described by ArQule's coworkers have shown that α,β-unsaturated ketones can play a pivotal role as branching points in a number of synthetic diversity schemes and therefore represent versatile intermediates for the efficient preparation of combinatorial heterocyclic libraries (e.g. isoxazolines, tetrahydropyrimidines or pyridines).[8] In an extension to this methodology, we have developed an efficient synthesis/purification strategy for the generation of *N*-substituted 2-pyrazolines.[9] This scaffold has been shown to have activity against a broad range of therapeutic targets (e.g. antibacterial, antiviral, and anti-inflammatory).[10]

In preparing prospective compound libraries for random screening it is desirable that the library introduces sufficient diversity to ensure a range of physicochemical properties for the library members.

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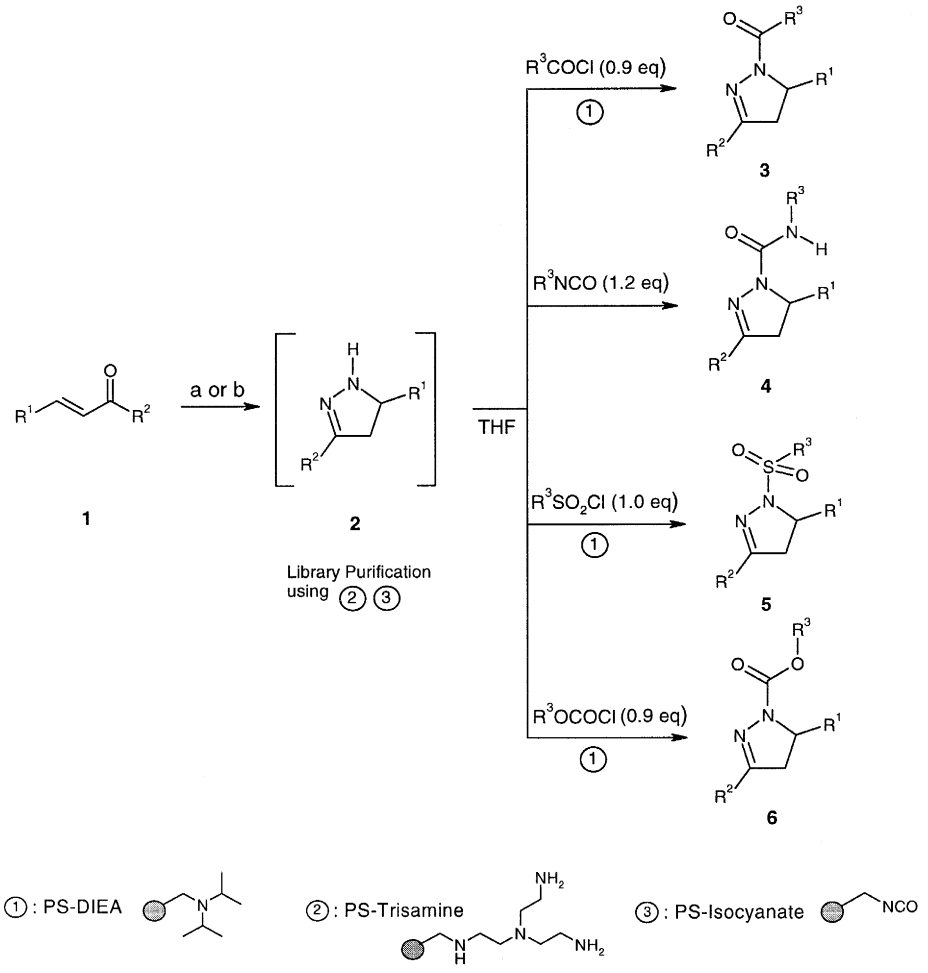
Our approach in designing prospective libraries is to include sets of compounds having drug-like characteristics (desirable molecular weight, good hydrophobic profile, moderate hydrogen bonding capacity) as well as compounds enriched with motifs that include biologically recognized functionalities and frameworks (privileged motifs). [11]

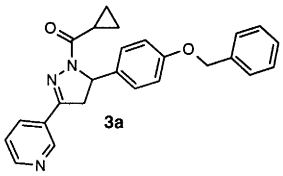
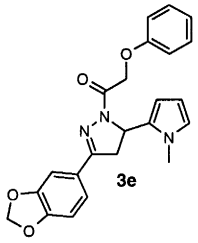
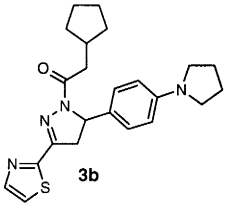
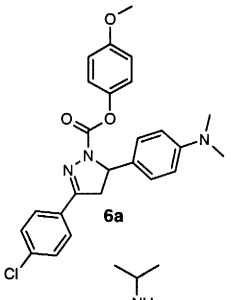
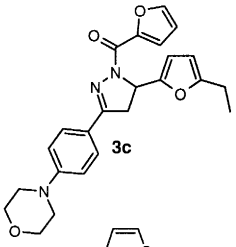
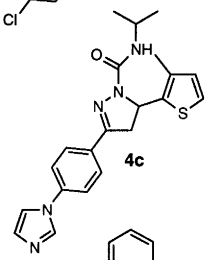
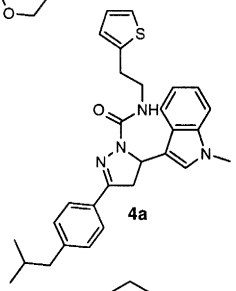
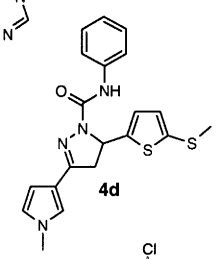
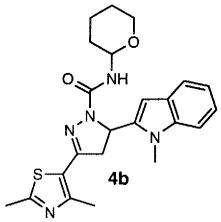
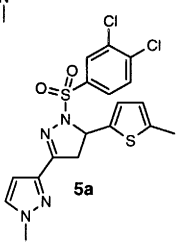
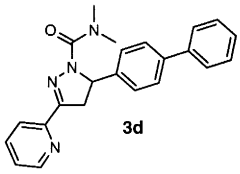
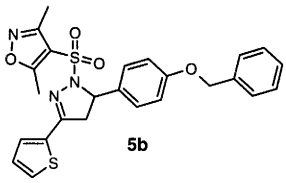
For the construction of a drug-like library based on the pyrazoline scaffold, we have selected a set of 80 chalcones of 'useful' diversity (balanced physicochemical characteristics enriched with privileged motifs) which were further manipulated using an approach that allows us to take full advantage of the large number of commercially available and diverse building blocks in both the aliphatic and aromatic/heteroaromatic categories. The resulting approach, as outlined in Scheme 1, involved the unique parallel synthesis of *N*-substituted 2-pyrazolines **3**–**6** via the intermediate **2**.[12] The selected chalcones **1** were readily prepared by aldol condensation of aryl/heteroaryl aldehydes with aryl/heteroaryl methylketones.[13]



Scheme 1. Reagents:[14](a) $N_2H_4 \cdot OH_2$ (1.05 equiv.), EtOH; 70°C, 3 h; (b) (i) $N_2H_4 \cdot OH_2$ (1.3 equiv.), EtOH; 70°C, 2 h; (ii) PSCHO, 70°C, 1 h

In a typical protocol, chalcone **1** and hydrazine monohydrate were heated at 70°C in EtOH for 3 h. The resulting unstable pyrazoline **2** was then trapped in the presence of a polymer-bound base (PS-DIEA) with electrophiles such as carbonyl chlorides (e.g. acid chlorides, chloroformates), isocyanates or

Table 1
Synthesis of various *N*-substituted 2-pyrazolines using polymer-supported reagents and scavengers

Product	Yield(%)[16]	Purity(%)[17]	Product	Yield(%)[16]	Purity(%)[17]
 **3a**	82	>95	 **3e**	89	91
 **3b**	80	88	 **6a**	75	88
 **3c**	87	85	 **4c**	65	76
 **4a**	78	80	 **4d**	84	91
 **4b**	87	89	 **5a**	87	89
 **3d**	75	82	 **5b**	78	91

sulfonyl chlorides for 12 h at room temperature to provide **3**–**6**. Treatment of **2** with sulfonyl chlorides required heating at 60°C for 6 h. A scavenging cocktail of polymer-supported isocyanate and trisamine was then added to sequester remaining pyrazoline **2** or excess electrophile, respectively. After quenching the reaction for 4 h, the product was isolated by filtration and evaporation. Representative products obtained from this one-pot protocol, along with the chemical yield and purity are shown in Table 1. The procedure appears widely applicable with a range of diverse electrophiles affording the corresponding pyrazolines **3**–**6** in good yields and purities.[15] Any concerns about the stability of the pyrazolines **3**–**6** were dismissed when attempts to oxidize **3**–**6** to the corresponding pyrazoles failed in our hands, even under reasonably harsh reaction conditions (e.g. DDQ, 110°C).

A library of over 1500 derivatives has been generated within 96-well plate format using the outlined approach. Several of these compounds have been identified as possessing biological activity within various therapeutic areas, a result that argues for the design approach taken.

In conclusion, we have devised a rapid and efficient route to *N*-substituted 2-pyrazolines by utilization of polymer-supported reagents and scavengers. The experimental procedure is simple, easy to automate and allows the fabrication of a broad range of diversity around the chalcone motif.

Acknowledgements

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14. Polymer-supported reagents/scavengers were purchased from Argonaut Technologies: PS-DIEA [*N*,*N*-(diisopropyl)aminomethyl polystyrene; capacity: 3.5 mmol/g]; PS-trisamine [*tris*-(2-aminoethyl)amine polystyrene; capacity: 3.45 mmol/g]; PS-isocyanate [polystyrene methylisocyanate; capacity: 1.55 mmol/g].
15. Representative experimental data for **5b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.42, 2.59 (s, 3H, CH_3); 3.15, 3.64 (dd, *J*=9 and 17 Hz, 1H, CH_2); 5.03 (dd, *J*=9 and 13 Hz, 1H, CH); 5.08 (s, 2H, OCH_2); 6.51 (dd, *J*=1.5 and 3.5 Hz, 1H), 6.78 (d, *J*=3.5 Hz, 1H), 6.96–7.55 (m, 10H) (Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.41, 13.16 (CH_3), 44.09 (CH_2), 64.16, 70.32 (CH, OCH_2), 112.30, 113.24, 113.64, 115.48, 127.70, 128.16, 128.29, 128.86, 132.51, 136.98, 145.35, 146.31, 148.94, 158.91, 159.02, 175.19 (=C, Ar–C).
16. Determination based on weight of crude sample. Control experiments have shown a good relationship between purity vs yield (e.g. **3a**: yield of pure (>95%) material: 82%; yield of purified material: 78%).
17. Purity determined by LC-MS analysis (DAD 220–350 nm; column: 4.6×50mm, Waters C8, 5 μm, 5 mL/min at 40°C; 1.5 or 3.5 min linear gradients from 0% to 100% MeCN with 5% MeCN in 0.01 M NH_4OAc buffer).