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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5289–5292

# A cyclative cleavage approach to solid-phase synthesis of annulated pyrimidinones using Baylis–Hillman derivatives☆

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Received 3 May 2005; revised 30 May 2005; accepted 8 June 2005

**Abstract**—An efficient and robust solid-phase synthesis of 6-substituted-2,5,6,8-tetrahydro-3*H*-imidazo[1,2-*a*]pyrimidin-7-ones, 3-substituted-1,3,4,6,7,8-hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones and 3-substituted-3,4,6,7,8,9-hexahydro-1*H*-pyrimido[1,2-*a*][1,3]diazepin-2-ones from the acetates of Baylis–Hillman adducts employing Michael addition of diamines followed by intramolecular cyclization with cyanogen bromide and, finally, base promoted cyclative cleavage has been developed. The procedure is validated through an automated parallel synthesis of a small library of fourteen compounds of the 3*H*-imidazo[1,2-*a*]pyrimidin-7-one series.


Solid-phase synthesis continues to hold a dominant position in combinatorial chemistry.[1] Over the last two decades, from a simple tool to prepare large number of compounds employing coupling chemistry, it has become a domain in its own right. The development and execution of different organic reactions on solid support has become the primary focus of several research groups and pharmaceutical organizations trying to increase the repertoire of synthetic reactions so as to provide novel compounds of biological significance. The presence of heterocyclic frameworks in drug structures, agrochemicals and natural products makes them attractive synthetic targets for combinatorial approaches using solid-phase strategies. In particular, nitrogen rich heterocycles have received greater attention due to their propensity to elicit broad ranges of biological activities.[2] As part of our research program aimed at the preparation of nitrogen-containing heterocycles utilizing Baylis–Hillman derivatives, we recently developed the synthesis of pyrrolidinone, pyrrolidine and 2-amino-1,4,5,6-tetrahydropyrimidines.[3,4] In particular, our interest in generating heterocyclic structures from Baylis–Hillman derivatives incorporating a cyclic guanidine pharmacophore led us to envisage the synthesis of substituted pyrimidinone derivatives through the sequential Michael addition of a diamine to the acetates of Baylis–Hillman adducts and the intramolecular cyclization of the diamine by cyanogen bromide followed by another intramolecular cyclization involving the amino and ester groups. Our initial efforts to carry out this chemistry in solution phase were unsuccessful since Michael addition of 1,2-diaminoethane invariably gave a polymeric product. Therefore, we decided to investigate a solid support for carrying out the desired synthesis.

The potential of the Baylis–Hillman reaction to yield useful synthons, heterocycles and natural products is now well established.[5] However, most of these successful transformations have been carried out using solution phase synthesis. There are only a few reports[6] on solid-phase approaches that utilize Baylis–Hillman derivatives towards these objectives. Described herein, is a cyclative cleavage procedure for the successful solid-phase synthesis of annulated pyrimidinone derivatives with two point diversity from the acetates of Baylis–Hillman adducts. To the best of our knowledge such annulated pyrimidinone derivatives are hitherto unreported in the literature. The synthetic methodology was validated through the automated synthesis of a fourteen-membered 6-substituted 3*H*-imidazo[1,2-*a*]pyrimidin-7-one library.

*Keywords*: Pyrimidinones; Baylis–Hillman; Solid-phase; Cyclative cleavage; Automation.
☆CDRI Communication No. 6772.
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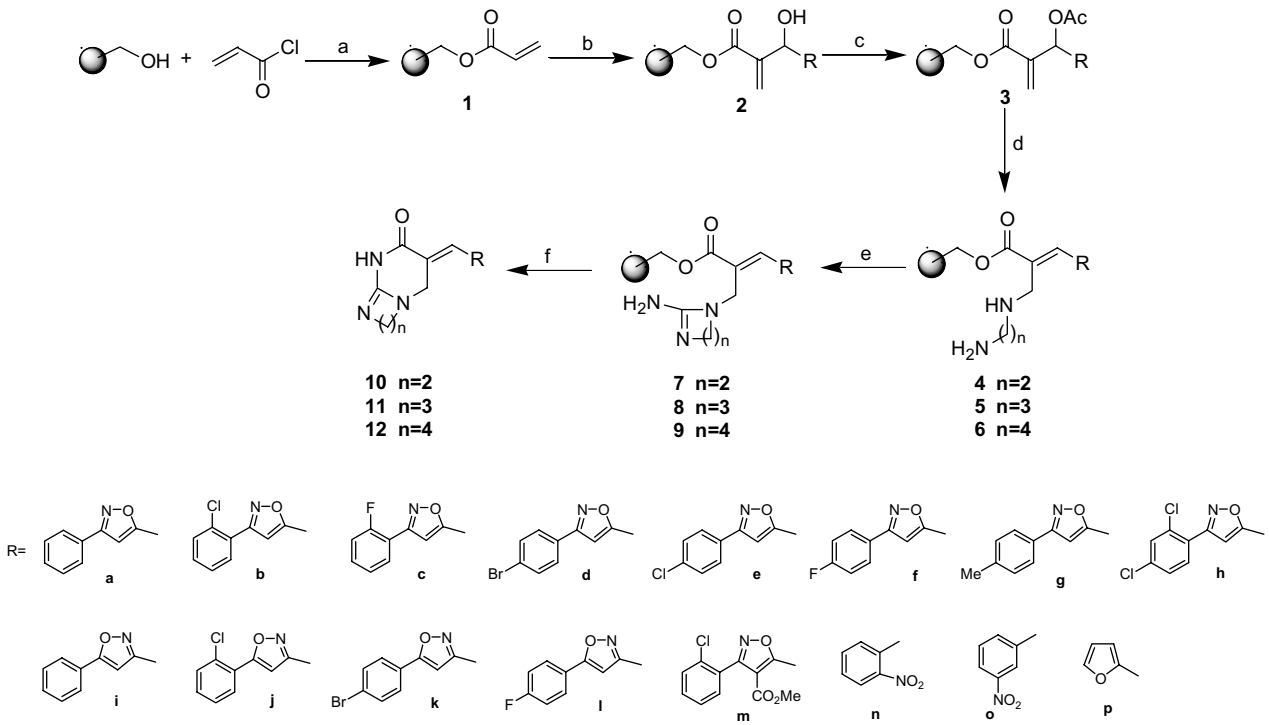
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.018




**Scheme 1.** Reagents and conditions: (a) Ref. 6; (b) RCHO, DABCO, DMSO, rt, 3 h; (c) AcCl, pyridine, $CH_2Cl_2$, rt, 16 h; (d) 1, *n*-diaminoalkane (*n* = 2–4), DMF, rt, 15 h; (e) CNBr, DMF–abs EtOH (1:1), rt, 12–30 h; (f) 20% $Et_3N$ in $CHCl_3$, reflux, 12 h.

The synthesis of the new pyrimidinone derivatives is outlined in Scheme 1. We selected the Wang resin as the solid support, since the ester group of the Wang acrylate resin was considered appropriate to carry out the basic cyclative cleavage of the acyclic resin-bound amine precursor to give the target compound. Therefore, in the first step the Wang acrylate resin **1** was prepared from acryloyl chloride and Wang resin (Novabiochem, 1.13 mmol/g) according to the literature procedure.[7] Treatment of the acrylate resin **1** with various aldehydes in the presence of DABCO in DMSO gave the Baylis–Hillman adducts **2** which were then transformed into acetates **3** in the presence of pyridine and acetyl chloride in dichloromethane. Subsequently, the acetates **3** were submitted to Michael addition in the presence of 1,2-diaminoethane at room temperature to give the allyl amine derivatives **4**, which were then cyclized with cyanogen bromide to yield the pyrazole derivatives **7** under standard conditions. The final cyclization and concomitant cleavage involving the amino group of the pyrazole nucleus and the ester of the resin to afford the pyrimidinone derivative **10** was induced in the presence of 20% triethylamine in chloroform under reflux. The final compounds **10** were obtained in good yields and purities.[8] All optimization reactions were carried out using *R* = **a**, **b** and **p** as the diversity elements. The optimization procedure was accompanied with on-bead FTIR, off-bead HPLC and ESMS analysis of the products at each step.

To install another point of diversity the same synthetic sequence was repeated with 1,3-diaminopropane and 1,4 diaminobutane in place of 1,2-diaminoethane. Treatment of the resin bound acetate **3** with 1,3-diaminopropane and 1,4-diaminobutane resulted in the allyl amine derivatives **5** and **6**, respectively. In contrast to the cyanogen bromide-mediated cyclization of allyl amine **4** within 14 h at room temperature, the allyl amines **5** and **6** underwent cyclization to afford the cyclized derivatives **8** and **9**, respectively, only after 24 h. Similar to substrate **7**, compounds **8** and **9** also underwent basic cyclative cleavage to yield the respective products **11** and **12** in good yields and purities.

The NMR of the crude products **10**–**12** revealed the presence of the *E*-isomers only, showing the singlet for the benzylic proton at around 7.00 ppm. Indeed this observation has precedence in the literature.[9]

In order to test the efficacy and robustness of this method for library production, we made a small library of 14 substituted 3*H*-imidazo[1,2-*a*]pyrimidin-7-ones (**10b**–**o**) (Table 1) through automation on MOS 496Ω (Advance ChemTech, USA). Indeed, all the products except for compound **10m** were obtained in good yields and purity. It is quite likely that the starting aldehyde for the corresponding product (**10m**) may not have undergone the initial Baylis–Hillman reaction in DMSO.[10]

In conclusion, we have demonstrated an efficient cyclative cleavage approach to the solid-phase parallel synthesis of new annulated pyrimidinone derivatives from easily accessible Baylis–Hillman products. The synthetic strategy described in this communication is robust enough to be translated through automation.

**Table 1.** Characterization data for new compounds

| Compound | Yield (%) | Purity (%) | HPLC[a] ($t_R$) (min) | ESMS ($M^+$) | HRMS {Found (calcd)} |
|---|---|---|---|---|---|
| **10a** | 65 | 92 | 14.1 | 295.13 ($M^+$+1) | 294.1102 (294.1117) |
| **10b** | 83 | 72 | 15.2 | 328.80, 350.93 ($M^+$+Na) | 328.0719 (328.0727) |
| **10c** | 73 | 97 | 15.0 | 312.93, 335.00 ($M^+$+Na) | 312.1024 (312.1023) |
| **10d** | 85 | 61 | 20.2 | 373.87 ($M^+$+1) | 372.0230 (372.0222) |
| **10e** | 71 | 72 | 14.4 | 328.35 | 328.0727 (328.0723) |
| **10f** | 73 | 96 | 13.9 | 313.27 ($M^+$+1), 335.13 ($M^+$+Na) | 312.1046 (312.1023) |
| **10g** | 92 | 87 | 16.9 | 309.20 ($M^+$+1), 330.93 ($M^+$+Na) | 308.1269 (308.1273) |
| **10h** | 60 | 65 | 16.3 | 363.87 ($M^+$+1) | 362.0339 (362.0337) |
| **10i** | 75 | 98 | 13.1 | 295.20 ($M^+$+1), 316.93 ($M^+$+Na) | 294.1119 (294.1117) |
| **10j** | 77 | 93 | 14.8 | 329.20 ($M^+$+1), 351.07 ($M^+$+Na) | 328.0729 (328.0723) |
| **10k** | 67 | 67 | 20.0 | 372.01, 395.32 | 372.0226 (372.0222) |
| **10l** | 94 | 98 | 14.0 | 313.13 ($M^+$+1) | 312.1022 (312.1023) |
| **10m** | — | — | — | — | — |
| **10n** | 86 | 71 | 12.2 | 273.13 ($M^+$+1) | ND |
| **10o** | 52 | 69 | 11.6 | 273.47 ($M^+$+1), 295.40 ($M^+$+Na) | ND |
| **10p** | 87 | 68 | 16.5 | 218.27 ($M^+$+1) | 217.0893 (217.0891) |
| **11a** | 62 | 87 | 14.4 | 309.13 ($M^+$+1) | 308.1277 (308.1273) |
| **11b** | 86 | 88 | 15.4 | 342.80 | 342.0880 (342.0884) |
| **11p** | 78 | 69 | 14.0 | 232.20 ($M^+$+1) | 231.1015 (231.1008) |
| **12a** | 75 | 88 | 17.4 | 323.20 ($M^+$+1) | 322.1427 (322.1430) |
| **12b** | 80 | 76 | 14.8 | 356.73 | ND |
| **12p** | 70 | 71 | 14.1 | 246.20 ($M^+$+1) | ND |

[a] HPLC was carried out on an Agilent 1100 system having a DA detector ($\lambda_{max}$ = 220 nm, 254 nm used for this study) using a gradient run of 0–100% acetonitrile in water containing 0.1% TFA over 30 min on a RP-18e column (250 × 4.6 mm) having a particle size of 5 μm. ND = not done.


## Acknowledgements

The financial assistance to two of the authors (R.P. and A.K.R.) from CSIR, New Delhi, in the form of fellowships is gratefully acknowledged. This work was supported through a financial grant under DST Project no. SR/SI/OC-04/2003.


## References and notes


1. (a) Dolle, R. E. *J. Comb. Chem.* **2004**, *6*, 623–679; (b) Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693–753; (c) Geysen, H. M.; Schoenen, F.; Wagner, D.; Wagner, R. *Nat. Rev. Drug Disc.* **2003**, *2*, 222–230.
2. (a) Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415–2437; (b) Kundu, B. *Curr. Opin. Drug Dev.* **2003**, *6*, 815–826.
3. Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353–356.
4. Pathak, R.; Roy, A. K.; Batra, S. *Synlett* **2005**, 848–850.
5. Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891, and references cited therein.
6. (a) Richter, H.; Jung, G. *Mol. Divers.* **1997–1998**, *3*, 191–194; (b) Richter, H.; Walk, T.; Höltzel, A.; Jung, G. *J. Org. Chem.* **1999**, *64*, 1362–1365; (c) Kulkarni, B. A.; Ganeshan, A. *J. Comb. Chem.* **1999**, *1*, 373–378; (d) Racher, R.; Doring, K.; Reiser, R. *J. Org. Chem.* **2000**, *65*, 6932–6939; (e) Batra, S.; Rastogi, S. K.; Kundu, B.; Patra, A.; Bhaduri, A. P. *Tetrahedron Lett.* **2000**, *41*, 5971–5974; (f) Rastogi, S. K.; Gupta, P.; Srinivasan, T.; Kundu, B. *Mol. Divers.* **2000**, *5*, 91–104; (g) Reiser, U.; Jauch, J. *Synlett* **2001**, 90–92.
7. Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708–718.
8. Experimental: To Wang acrylate resin[6] (100 mg in a polypropylene syringe) prepared from Wang resin (Novabiochem, 1.13 mmol/g) in 800 μL DMSO was added 3 equiv of DABCO. After 15 min of shaking a solution of substituted 5-isoxazolecarboxaldehyde (**a**) (5.0 equiv) in 500 μL of DMSO was added to the reaction vessel. The resulting mixture was shaken at 600 rpm for 3 h. Subsequently, the resin was washed with DMF (×3), MeOH (×3), $CH_2Cl_2$ (×3) and diethyl ether (×2). The resin was dried over $P_2O_5$ under vacuum. The dried resin-bound adduct **2** was taken up in a glass vessel in anhydrous $CH_2Cl_2$ (2 mL). To this was added pyridine (8 equiv) followed by the dropwise addition of acetyl chloride (16 equiv in 300 μL of $CH_2Cl_2$) at 0 °C. The reaction mixture was stirred for 16 h, after which it was transferred to syringe and washed with $CH_2Cl_2$ (×1), DMF (×2), MeOH (×2) and $CH_2Cl_2$ (×3). The resin bound acetate was suspended in DMF (1.5 mL) and treated with 10 equiv of 1,2-diaminoethane. The reaction mixture was shaken for 15 h at 600 rpm at room temperature. Thereafter, the reaction mixture was washed as usual, dried and suspended in DMF–abs EtOH mixture (1:1, v/v, 1.5 mL). It was next treated with 4 equiv of cyanogen bromide and the reaction was shaken for 14 h (30 h for 1,3-diaminopropane and 1,4-diaminobutane) at 600 rpm at room temperature. The resin was once again washed as usual and dried thoroughly over $P_2O_5$ under vacuum. The resin was treated with a 20% solution of $Et_3N$ in anhydrous $CHCl_3$ (4 mL) under reflux for 15 h. Then the resin was filtered and the filtrate was washed with water, dried and evaporated to give the final crude product, which was lyophilized using *tert*-butanol–water (4:1, v/v, 4 mL). Representative data—compound **10j**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.87 (t, 2H, $J$ = 6.4 Hz), 3.15 (t, 2H, $J$ = 6.4 Hz), 3.48 (s, 2H), 6.91 (s, 1H), 7.12 (s, 1H), 7.36–7.65 (m, 3H), 7.82–7.89 (m, 1H). Compound **11b**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.36–1.43 (m, 2H), 2.51–2.63 (m, 2H), 3.49 (s, 2H), 3.68–3.77 (m, 2H), 6.61 (s, 1H), 6.85 (s, 1H), 7.31–7.39 (s, 2H), 7.46–7.48 (m, 1H), 7.68–7.71 (m, 1H). Compound **11p**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.41–1.45 (m, 2H), 2.52–2.65 (m, 2H), 3.14–3.17 (m, 2H), 3.65 (s, 2H), 5.60 (s, 1H), 6.24 (s, 1H), 7.44 (s, 1H), 7.62 (d, 1H, $J$ = 3.9 Hz). Compound **12b**: $^1$H NMR ($CDCl_3$, 300 MHz)

$\delta$ 1.36–1.47 (m, 4H), 2.61–2.65 (m, 2H), 3.49 (s, 2H), 3.82–3.94 (m, 2H), 6.65 (s, 1H), 7.01 (s, 1H), 7.31–7.40 (m, 2H), 7.47–7.49 (m, 1H), 7.69–7.71 (m, 1H).

9. (a) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, 403–408; (b) Lee, J. L.; Chung, Y. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2000**, *21*, 843–844; (c) Batra, S.; Roy, A. K.; Patra, A.; Bhaduri, A. P.; Surin, W. S.; Raghvan, S. A. V.; Sharma, P.; Kapoor, K.; Dikshit, M. *Bioorg. Med. Chem.* **2004**, *12*, 2059–2077.
10. Batra, S.; Roy, A. K. *Synthesis* **2004**, 2550–2554.