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Aldol Reactions in Multicomponent Reaction Based Domino Pathways: A Multipurpose Enabling Tool in Heterocyclic Chemistry

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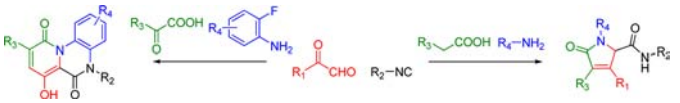
ABSTRACT



The aldol reaction has been evaluated in combination with the Ugi multicomponent reaction to assemble richly decorated mono- and polycyclic systems via expeditious cascade pathways. A small collection of pyrrolinones was generated thereof, and the scarcely accessible pyridoquinoxalinedione scaffold was also prepared by designing an additional nucleophilic substitution step in this domino sequence requiring minimal operational effort.

Since the infancy of synthetic organic chemistry, significant efforts have been devoted to the discovery of methodologies for the preparation of heterocyclic compounds. Shortly after the structures of the fundamental heterocycles were elucidated, one of the first goals of the scientific community was the development of routes to assemble such moieties from materials accessible at the time.[1] Since that pioneering age, activity in this field has proceeded unabated taking advantage of an arsenal of methodology advancements made available over the past century.[2] Today, two main trends that followed in the broad area of heterocyclic chemistry are the use of cycloaddition-based strategies[3] and transition-metal-mediated annulations.[4] However, a very convenient and expeditious strategy that has emerged as a viable alternative is represented by multicomponent reactions (MCRs)[5] followed by post-condensation modifications.[6] MCRs combine three or more reagents in a one-pot process, affording in a single step and under typically simple experimental conditions a final product containing portions derived from each of the reacting molecules. Postcondensation modifications, which are subsequent transformations taking

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(1) For examples of these early reports, see: (a) For furan: Limpricht, H. *Chem. Ber* **1870**, *3*, 90. (b) For pyrrole: Hantzsch, A. *Chem. Ber*. **1890**, *23*, 1474. (c) For thiophene: Volhard, J.; Erdmann, H. *Chem. Ber*. **1885**, *18*, 454. (d) For pyridine: Hantzsch, A. *Chem. Ber*. **1881**, *14*, 1637. (e) For quinoline: Skraup, Z. H. *Chem. Ber*. **1880**, *13*, 2086. (f) For indole: Baeyer, A.; Emmerling, A. *Chem. Ber*. **1869**, *2*, 679.

(2) For excellent reviews on the topic, see: (a) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev*. **2007**, *36*, 1095. (b) Alvarez-Corral, M.; Muñoz-Dorado, M.; Rodrıguez-Garcia, I. *Chem. Rev*. **2008**, *108*, 3174. (c) Patil, N. T.; Yamamoto, Y. *Chem. Rev*. **2008**, *108*, 3395. (d) Molander, G. A. *Acc. Chem. Res*. **1998**, *31*, 603. (e) Chiba, S. *Synlett* **2012**, 21.

(3) (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley & Sons: Hoboken, NJ, 2002. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev*. **1996**, *96*, 49. (c) Chiacchio, U.; Padwa, A.; Romeo, G. *Curr. Org. Chem*. **2009**, *13*, 422.

(4) (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev*. **2004**, *104*, 2285. (c) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265.

(5) For example, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymè, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev*. **2012**, *112*, 3083. (c) Sunderhaus, J. D.; Martin, S. E. *Chem.—Eur. J*. **2009**, *15*, 1300. (d) Hulme, C.; Dietrich, J. *Mol. Diversity* **2009**, *13*, 195. (e) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed*. **2011**, *50*, 6234. (f) *Synthesis of Heterocycles via Multicomponent Reactions*; Ruijter, E., Orru, R. V. A., Eds.; Springer-Verlag: Berlin, Germany, 2010. (g) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev*. **2010**, *39*, 4402.

(6) For the importance of post-condensation modifications, see: Ayaz, M.; De Moliner, F.; Dietrich, J.; Hulme, C. *Evolution of Isocyanide Chemistry*; Nenajdenko, V., Ed.; Wiley-VCH: Weinheim, Germany, 2012.

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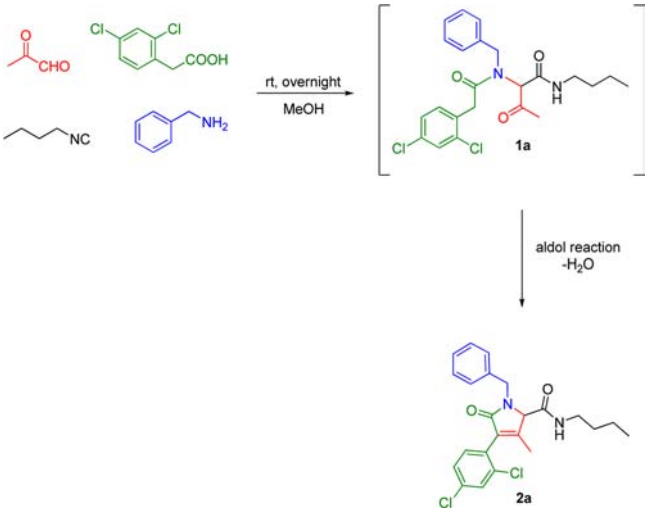
place after the MCR, are in turn able to rigidify the often acyclic multicomponent adducts into a number of cyclic species. As such, multicomponent approaches are ideal to address some of the drawbacks affecting classical heterocyclic syntheses, such as poor availability of starting materials or the need for difficult, lengthy, and elaborate synthetic operations.[7] Our group has significant experience in the design of novel chemotypes *via* these kinds of pathways, as exemplified by reports dealing with the preparation of quinoxalines, benzodiazepines, benzimidazoles, pyrrolidinones, and pyrazoles, *inter alia*.[8]

Inspired by our recent findings on the applicability of aldol reactions to the development of domino sequences[9] and with the intent of devising new straightforward one-pot strategies to enrich the heterocyclic chemistry toolbox, we embarked on a campaign to investigate the possibilities suggested by this approach. Initially, we turned our attention to the synthesis of the pyrrolinone moiety, a very appealing biological scaffold shown to be a key motif in HIV-1 integrase inhibitors,[10] peptidomimetics,[11] and marine natural products possessing relevant antibacterial properties, such as holomycine[12] and tetramic acids.[13]

The assembly of the acyclic precursor for this chemotype was accomplished by means of the Ugi four-component condensation (U-4CR),[14] which predictably performed well under the classical mild conditions.[15] Pyruvic aldehyde, *n*-butylisonitrile, 2,4-dichlorophenylacetic acid, and benzylamine were mixed in methanol and stirred overnight at room temperature. Upon formation of **1a**, the solvent was removed and the crude residue was subjected to the aldol reaction without any purification. On the basis of our recent work,[9] microwave irradiation at elevated temperatures and 2 equiv of organic bases were employed to trigger the cyclization step. Different temperatures, reaction times, and solvents were next evaluated (Table 1), and heating at 160 °C for 20 min in DMF in the presence of diisopropylamine (DIPA, entry 2) proved optimal, smoothly affording cyclized product **2a** in a very satisfactory 75% yield over two steps.

Table 1. Optimization of the Cyclization Step in the Ugi–Aldol Sequence



entry	solvent	base	temp (°C)	time (min)	yield (%)
1	DMF	DIPA	140	20	56
2	DMF	DIPA	160	20	75
3	DMF	DIPA	160	40	57
4	DMF	TEA	160	20	57
5	DMSO	DIPA	160	20	43
6	THF	DIPA	160	20	50

With optimized conditions for the second step of the sequence in hand, we thus investigated the use of different starting materials in order to determine the reactivity domain of the Ugi–aldol two-step, one-pot route and to assemble a small collection of compounds of generic structure **2**. Overall, two glyoxaldehydes, three isonitriles, four carboxylic acids, and eight amines were employed to build a representative set (Table 2) with yields of **2a**–**2i** spanning 62–82%, requiring only column chromatography of the final product.

The advantages of the multicomponent approach to the synthesis of **2** over conventional linear methodologies are numerous. In fact, reported stepwise protocols for the preparation of pyrrolinones mostly involve the use of exotic starting materials, transition metal catalysts, and/or lengthy multistep routes and suffer from a resulting lack of generality and practical ease.[16] The strategy described herein also differs from the existing multicomponent protocols leading to this chemotype, which either are unable to render final products with four diversity points[17] or rely

(7) For significant examples of this approach to the synthesis of heterocycles, see: (a) Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repetto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151. (b) Wang, W.; Ollio, S.; Herdtweck, E.; Dömling, A. *J. Org. Chem.* **2011**, *76*, 637. (c) Znabet, A.; Zonneveld, J.; Janssen, E.; De Kanter, F. J. J.; Helliwell, M.; Turner, N. J.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2011**, *46*, 7706. (d) Erb, W.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 3109. (e) El Kaim, L.; Gizolme, M.; Grimaud, L. *Synlett* **2007**, 227. (f) De Moliner, F.; Crosignani, S.; Galatini, A.; Riva, R.; Basso, A. *ACS Comb. Sci.* **2011**, *13*, 453.

(8) For example, see: (a) De Moliner, F.; Hulme, C. *Org. Lett.* **2012**, *14*, 1354. (b) De Moliner, F.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 5787. (c) Gunawan, S.; Ayaz, M.; De Moliner, F.; Frett, B.; Kaiser, C.; Patrick, N.; Hulme, C. *Tetrahedron* **2012**, *68*, 5606. (d) Shaw, A. Y.; Medda, F.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1313. (e) Xu, Z.; Ayaz, M.; Cappelli, A. P.; Hulme, C. *ACS Comb. Sci.* **2012**, *14*, 460. (f) Gunawan, S.; Petit, J.; Hulme, C. *ACS Comb. Sci.* **2012**, *14*, 160. (g) Shaw, A. Y.; McLaren, J. A.; Nichols, G S.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 2592.

(9) Xu, Z.; De Moliner, F.; Cappelli, A. P.; Hulme, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8037.

(10) (a) Pace, P.; Spieser, S. A. H.; Summa, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3865. (b) Ma, K.; Wang, P.; Fu, W.; Wan, X.; Zhou, L.; Chu, Y.; Ye, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6724.

(11) Raghuraman, A.; Ko, E.; Perez, L. M.; Ioerger, T. R.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133*, 12350.

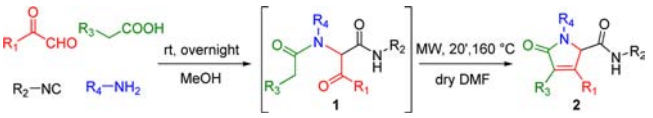
(12) (a) Wietz, M.; Mansson, M.; Gotfredsen, C. H.; Larsen, T. O.; Gram, L. *Mar. Drugs* **2010**, *8*, 2946. (b) Hjelmgaard, T.; Givskov, M.; Nielsen, J. *Org. Biomol. Chem.* **2007**, *5*, 344.

(13) (a) Ueda, C.; Tateda, K.; Horikawa, M.; Kimura, S.; Ishii, Y.; Nomura, K.; Yamada, K.; Suematsu, T.; Inoue, Y.; Ishiguro, M.; Miyairi, S.; Yamaguchi, K. *Antimicrob. Agents Chemother.* **2010**, *54*, 683. (b) Holloway, C. A.; Matthews, C. J.; Jeong, Y.-C.; Moloney, M. G.; Roberts, C. F.; Yaqoob, M. *Chem. Biol. Drug Des.* **2011**, *78*, 229.

(14) Ugi, I.; Steinbruckner, C. *Angew. Chem.* **1960**, *72*, 267.

(15) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632.

Table 2. Scope of the Ugi–Aldol Sequence toward Pyrrolinones **2**



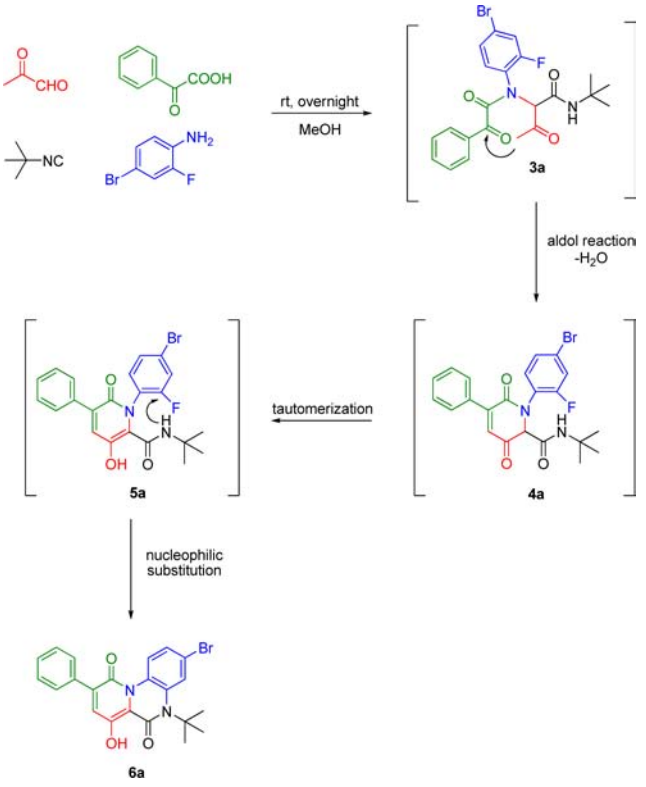
compd	R_1	R_2	R_3	R_4	yield (%)
2a	Me	*n*-Bu	2,4-di-Cl-Ph	Bn	75
2b	Me	*n*-Bu	2,4-di-Cl-Ph	2,4-di-MeO-Ph	68
2c	Me	*n*-Bu	2,4-di-Cl-Ph	2-furylmethyl	62
2d	Me	Bn	3,4-di-MeO-Ph	3,4-di-MeO-Ph	82
2e	Me	*n*-Bu	3,5-di-F-Ph	2-Cl-Bn	73
2f	Ph	*n*-Bu	3,5-di-CF_3-Ph	Bn	67
2g	Ph	*n*-Bu	3,5-di-CF_3-Ph	4-Br-Ph	72
2h	Ph	*n*-Bu	3,5-di-F-Ph	4-Cl-Ph	77
2i	Ph	*i*-Pr	3,4-di-MeO-Ph	Bu	79

on scarcely available phosphorus-containing building blocks.[18]

Enticed by the potential of this method and interest in the design of straightforward domino pathways for the synthesis of unusual polyheterocyclic frameworks, it was envisioned that a tandem approach encompassing an aldol condensation and a nucleophilic aromatic substitution[19] could pave the way to the assembly of pyridoquinoxalinediones **6** (Table 3).

In this case, the nucleophilic partner in the aldol reaction was furnished by pyruvic aldehyde. Completing the functionality for the desired cascade reaction, a fluorine atom installed on the aniline input of the MCR was expected to be displaced upon nucleophilic attack by the amidic nitrogen embedded in the Ugi backbone. *tert*-Butylisonitrile, phenylglyoxylic acid, 2-fluoro-4-bromoaniline, and pyruvic aldehyde were thus evaluated by simple mixing in methanol and subsequent stirring overnight at rt. After removal of the solvent, crude **3a** was subjected to thermal treatment in the presence of a base, which promoted an aldol-driven cyclization to **4a** followed by tautomerization.

Table 3. Optimization Studies in the Cascade Route Leading to Pyridoquinoxalinediones



entry	solvent	base	temp[a] (°C)	time	yield (%)
1	DMF	DIPA	160	20 min	10
2	DMF	DIPA	140	20 min	10
3	DMF	DIPA	180	20 min	33
4	DMF	K_2CO_3	180	20 min	26
5	DMF	$CsCO_3$	180	20 min	17
6	DMF	DIPA	120	overnight	70
7	DMF	K_2CO_3	120	overnight	47
8	DMF	$CsCO_3$	120	overnight	29

[a] Microwave irradiation was employed except for entries 10–12.

A second ring closure taking place in a one-pot fashion thus provided final tricyclic species **6a** *via* intermediate **5a**. This constitutes a nonobvious four-step pathway, giving access to an otherwise challenging structure by means of two easy synthetic operations with only one chromatographic exercise (entry 1, Table 3) albeit in this case in only 10% overall yield.

Further optimization studies for the double cyclization step of this cascade were thus conducted (Table 3). Hence, lower or higher temperatures gave similar unsatisfactory outcomes (entries 2 and 3), and evaluation of potassium and cesium carbonate also proved unfruitful (entries 4 and 5). Gratifyingly, conventional heating overnight in an oil bath in the presence of DIPA afforded **6a** in 70% yield over four steps in one pot (entry 6). It is worth noting that this represents a high-yielding and experimentally straightforward domino sequence affording an uncommon tricyclic

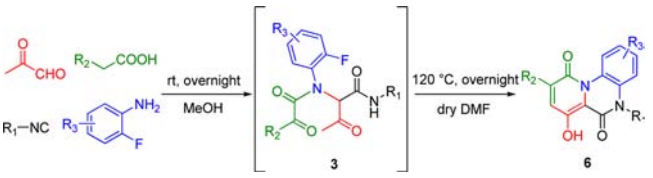
(16) For some examples, see: (a) Auricchio, S.; Truscello, A. M.; Lauria, M.; Meille, S. V. *Tetrahedron* **2012**, *68*, 7441. (b) Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Nishii, T.; Shishido, K. *Chem.—Eur. J.* **2006**, *12*, 524. (c) Ozawa, T.; Horie, H.; Kurahashi, T.; Matsubara, T. *Chem. Commun.* **2010**, *46*, 8055. (d) Daly, M.; Gill, K.; Sime, M.; Simpson, G. L.; Sutherland, A. *Org. Biomol. Chem.* **2011**, *9*, 6761. (e) Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 10214. (f) Greger, J. G.; Yoon-Miller, S. J. P.; Bechtold, N. R.; Flewelling, S. A.; MacDonald, J. P.; Downey, C. R.; Cohen, E. A.; Pelkey, E. T. *J. Org. Chem.* **2011**, *76*, 8203.

(17) (a) Basso, A.; Banfi, L.; Galatini, A.; Guanti, G.; Rastrelli, F.; Riva, R. *Org. Lett.* **2009**, *11*, 4068. (b) Fukuyama, T.; Nakashima, N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* **2012**, *135*, 1006. (c) Ryabukhin, S. V.; Panov, D. M.; Plaskon, A. S.; Grygorenko, O. O. *ACS Comb. Sci.* **2012**, *14*, 631.

(18) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39.

(19) For the use of nucleophilic aromatic substitutions to manipulate Ugi adducts, see: (a) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963. (b) Trifilenkov, A. S.; Ilyin, A. P.; Kysil, V. M.; Sandulenko, Y. B.; Ivachtchenko, A. V. *Tetrahedron Lett.* **2007**, *48*, 2563. (c) Spatz, J. H.; Umkehrer, M.; Kalinski, C.; Ross, G.; Burdack, C.; Kolb, J.; Bach, T. *Tetrahedron Lett.* **2007**, *48*, 8060. (d) Cristau, P.; Vors, J.-P.; Zhu, J. *QSAR Comb. Sci.* **2006**, *25*, 519. (e) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079.

Table 4. Scope of the Cascade Route toward Compounds **6**



compd	R_1	R_2	R_3	yield (%)
6a	*t*-Bu	Ph	4-Br	70
6b	4-MeO-Ph	Ph	H	50
6c	2,5-di-Me-Ph	2-furyl	H	73
6d	*n*-Bu	Ph	H	66
6e	*t*-Bu	2-thienyl	4-Cl	77
6f	2,5-di-Me-Ph	Ph	4-Cl	75
6g	*n*-Bu	2-thienyl	H	62
6h	*i*-Pr	2-thienyl	4-Cl	56

scaffold, previously prepared by relatively inferior methods.[20]

Again, the scope of the protocol was explored, and five isonitriles, three carboxylic acids, and three anilines were evaluated (Table 4), enabling production of a small collection of eight compounds **6** with yields ranging from 50% to 77%.

In conclusion, we have demonstrated herein the potential possessed by the sequential combination of the Ugi four-component reaction with the aldol condensation. In this vein, two straightforward and operationally friendly domino pathways enabling the rapid assembly of the heterocyclic cores **2** and **6** were elaborated. This methodology is diversity-enabling and suitable for the expeditious preparation of complex molecular frameworks when additional chemical transformations are embedded in the cascade. We hope this method will represent a valuable tool in heterocyclic chemistry.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **2** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) (a) Yavari, A.; Souri, S.; Sirouspour, M.; Bayat, M. J. *Synlett* **2009**, 1921. (b) Akbarzadeh, R.; Tayebeh, A.; Mirzaei, P.; Bazgir, A. *Helv. Chim. Acta* **2011**, *94*, 1527.