JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

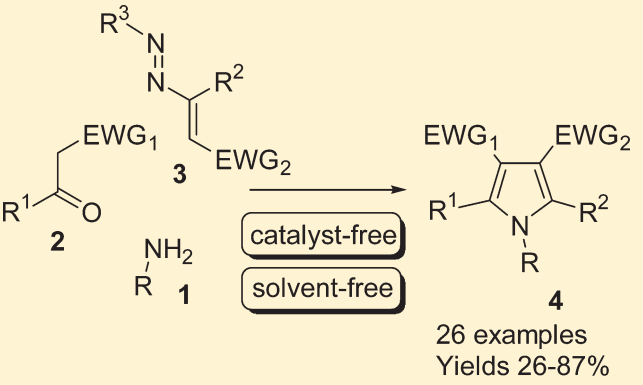
Synthesis of Functionalized Pyrroles via Catalyst- and Solvent-Free Sequential Three-Component Enamine−Azoene Annulation

Orazio A. Attanasi, Gianfranco Favi,* Fabio Mantellini, Giada Moscatelli, and Stefania Santeusanio

Istituto di Chimica Organica, Università degli Studi di Urbino "Carlo Bo", Via I Maggetti 24, 61029 Urbino, Italy

Supporting Information

ABSTRACT: A new and efficient synthesis of polysubstituted pyrroles by a sequential one-pot three-component reaction between primary aliphatic amines, active methylene compounds, and 1,2-diaza-1,3-dienes (DDs) is reported. The reactions were performed without catalyst and under solvent-free conditions with complete control of pathway selectivity. Notably, the ready availability of the starting materials and the high level of practicability of the reaction and work up make this approach an attractive complementary method for access to unknown polysubstituted pyrroles.



INTRODUCTION

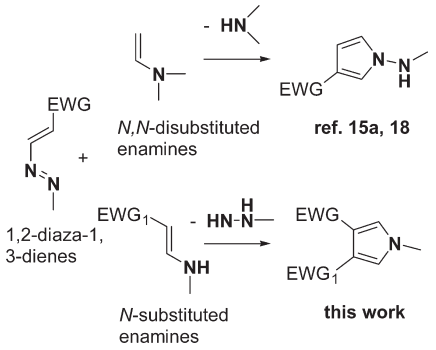
The rapid assembly of complex molecules from simple precursors in a one-pot procedure has attracted the interest of the organic chemistry community over recent decades. In this regard, sequential processes[1−3] that incorporate "green chemistry" values such as atom, time, and labor economies, resource management, and minimal chemical waste generation maintain a privileged status. Because of the importance of heterocycle-based compounds including biologically active agents, components in polymers, and intermediates, pyrroles[4] are considered one of the most important classes. Accordingly, substantial attention has been paid to developing efficient methods for their synthesis. The most frequently used methods include the classical Hantzch procedure,[5] the cyclocondensation of α-aminoketones with β-ketoester or β-diketones (Knorr synthesis),[6] the cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal−Knorr synthesis),[7] and various cycloaddition and transition-metal-catalyzed cyclization strategies.[8,9] Many of these procedures, however, have certain restrictions in terms of the scope and placement of the substitution pattern around the heterocycle core. We were surprised to discover that relatively few methods for the synthesis of the 3,4-EWG-substituted pyrrole system exist in the literature considering the importance, for example, of pyrrole-3,4-dicarboxylic acid derivatives in medicinal and material/surface attachment chemistry.[9,10] In addition, many of these reaction conditions require the use of high temperature or the presence of strong bases/acids and metal catalysts or produce non-negligible byproducts.

Enamines are valuable structures in organic synthesis.[11−13] They are extensively employed as nucleophiles in Michael-type additions, intermediates in the synthesis of heterocycles and natural products, and precursors of chiral amines upon asymmetric transformations. Among them, β-enaminones and related compounds represent versatile and useful building blocks for the construction of heterocyclic scaffolds, such as pyrrole, pyrazole, piperidine, 1,4-dihydropyridine, pyridinone, pyrimidine, isoxazole, indole, 1,5-benzodiazepine, quinoline derivatives, etc.[12,13]

On the other hand, the potential value of the 1,2-diaza-1,3-dienes (DDs)[14] in synthetic chemistry is derived mainly from their ready availability and unique reactivity. The chemistry of DDs, especially their behavior with various secondary enamines (used as enolate equivalents), has been a well-investigated area of research over the years. Earlier works reported by Sommer account for [3 + 2] and [4 + 2] cycloaddition reactions of several 4-alkoxycarbonyl-DDs with cyclopentanone-derived enamines and 9-vinylcarbazole, giving rise, in low to moderate yields, to octahydro-cyclopenta[*b*]indole and 9-pyridazin-3-yl-9*H*-carbazole.[15] South et al. reported the synthesis and reactions of 4-chloro- or 4,4-dichloro-DDs as a new and general method for access to 1,2,5,6-tetrahydropyridazines.[16] In addition, regio- and stereoselective one-pot protocols for the synthesis of highly functionalized 1-aminopyrrolines and oxazoline-fused 1-aminopyrrolines or oxazoline-fused pyridazines have been reported starting from 4-alkoxycarbonyl- or 4-chloro-DDs and 3-dimethylaminopropenoates.[17] Finally, a solvent-dependent, divergent synthesis of various functionalized pyrroles and pyridazines starting from 4-alkoxycarbonyl-DDs with enamines β-, β,β-, and α,β-substituted with simple alkyl and/or aryl groups was also described.[18]

Received: February 7, 2011
Published: March 11, 2011

Scheme 1. Formation of Pyrroles by Different Aza-annulation Reactions of Primary and Secondary Enamines



A stepwise mechanism that explains the results obtained in [3 + 2] cycloaddition reactions of simple secondary enamines with DDs was reported to involve a transient zwitterionic hydrazone intermediate generated by C-nucleophilic attack of the enamines at the terminal carbon of the azo−ene system.[15a,17b,18] Starting from all these results, we hypothesized that a chemo- and regioselective reaction of the *N*-alkylenamine-derived zwitterionic intermediate could provide a new synthetic pathway for *N*-alkylaminopyrrole derivatives.

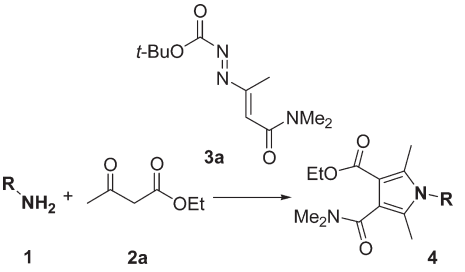
Thus, we were intrigued by the possible use of the N-substituted enamines (β-stabilized with electron-withdrawing groups (EWG_1) (e.g., CO_2R, $CONR_2$, COSR, SO_2R, $PO(OR)_2$) instead of N,N-disubstituted enamines as a bidentate nucleophile for aza-annulation reaction with DDs (Scheme 1).

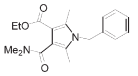
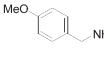
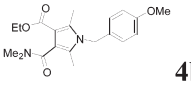
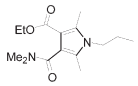
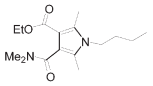
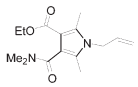
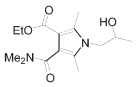
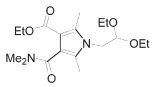
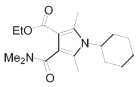
As part of our ongoing research program aimed at developing metal-free, multicomponent, and diversity-oriented domino-based syntheses of biologically relevant heterocycles, we report here a novel, multistep, three-component reaction of primary aliphatic amines, active methylene compounds, and DDs for the synthesis of highly functionalized pyrroles.[19] In this one-pot assembly, two independent reactions should occur sequentially: a condensation of 1,3-dicarbonyl compounds with amines to produce *N*-alkylenamine compounds, and an aza-annulation process to generate pyrrole derivatives through stepwise C-alkylation (Michael addition) and N-condensation of the enamine functionality with DDs.

RESULTS AND DISCUSSION

To realize a single-pot process by subsequent addition of reactants, we first developed the preparation of enamino intermediates. Although this transformation has been reported to proceed in the presence of various Brønsted or Lewis acids,[20] we found that it occurred well also in the absence of catalyst by using solvent-free conditions. In fact, treatment of benzylamine **1a** with ethyl acetoacetate **2a** under neat conditions at room temperature produced the corresponding enamino ester $\mathbf{A_I}$ in exclusively *Z* form[21] (see Supporting Information). The ^{1}H NMR spectra of the crude reaction mixture were very clean, indicating that the reaction took place quantitatively. As the next step, we attempted to combine the enamino ester formation with the subsequent aza-annulation process. After formation of the corresponding enaminone compound from benzylamine **1a** and ethyl acetoacetate **2a**, 1.0 equiv of DD **3a** was added directly to the reaction mixture under the same reaction conditions. To our delight, after the mixture was stirred 10 min at room temperature, the desired pyrrole **4aaa** was obtained in 65% yield without appreciable formation of dectable byproduct (Table 1, entry 1). With optimized reaction conditions in hand, we next examined the scope and limitation of this reaction. At first, various primary aliphatic amines such as (4-methoxybenzyl)amine **1b**, *n*-propylamine **1c**, *n*-butylamine **1d**, allylamine **1e**, 1-amino-2-propanol **1f**, 1-amino 2-acetaldehyde diethyl acetal **1g**, and cyclohexylamine **1h** were used and effectively converted into the corresponding substituted pyrroles **4(b−h)aa**. Substantially, the nature of the used amines had little influence on the reaction efficiency, and generally excellent yields were obtained (Table 1, entries 1−8).

Table 1. Amine Scope in the Synthesis of Pyrroles 4[a]



entry	1	Product 4	Yield (%)[b]
1	 **1a**	 **4aaa**	65
2	 **1b**	 **4baa**	56
3	 **1c**	 **4caa**	75
4	 **1d**	 **4daa**	74
5	 **1e**	 **4eaa**	67
6	 **1f**	 **4faa**	84
7	 **1g**	 **4gaa**	71
8	 **1h**	 **4haa**	61

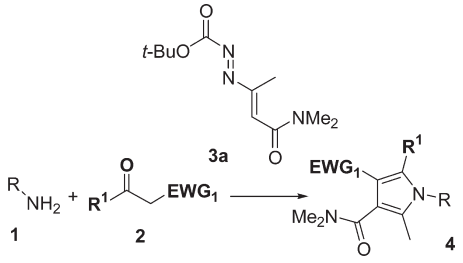
[a] For experimental details, see Supporting Information. [b] Yield of pure isolated products.

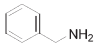
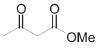
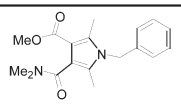
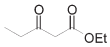
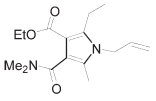
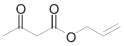
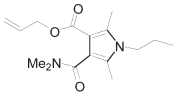
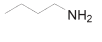
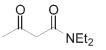
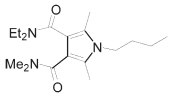
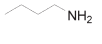
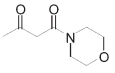
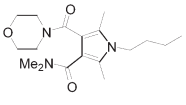
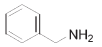
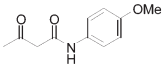
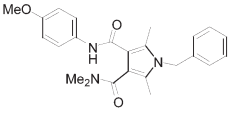
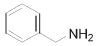
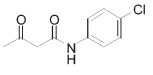
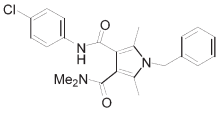
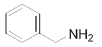
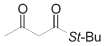
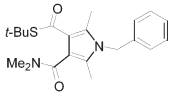
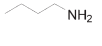
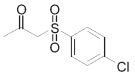
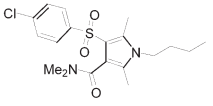
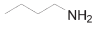
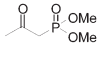
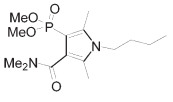
Because the activity of aromatic amines was lower than that of aliphatic amines in the aza-heterocyclization, unfortunately, the reactions with both electron-deficient/electron-rich substituent-containing anilines (R = Ph, *p*-Me(C_6H_5), *p*-OMe(C_6H_5), *p*-Br(C_6H_5)) did not provide the pertinent pyrroles.

Moreover, to expand the scope of this reaction with respect to active methylene substrates, a range of active methylene compounds **2b**−**l** containing ketone groups were surveyed for this

dx.doi.org/10.1021/jo200287k |*J. Org. Chem.* 2011, 76, 2860–2866

Table 2. Active Methylene Compounds Scope in the Synthesis of Pyrroles 4[a]



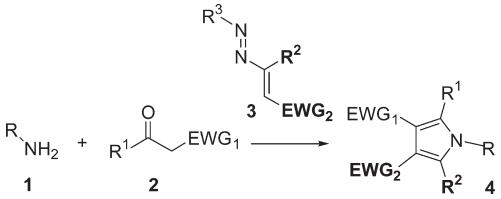
entry	1			2		Product 4		Yield (%)[b]
1		1a		2b		4aba		71
2		1e		2c		4eca		49
3		1c		2d		4cda		57
4		1d		2e		4dea		67
5		1d		2f		4dfa		83
6		1a		2g		4aga		58
7		1a		2h		4aha		69
8		1a		2j		4aja		75
9		1d		2k		4dka		26
10		1d		2l		4dla		41

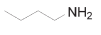
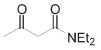
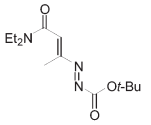
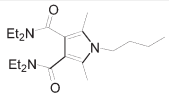
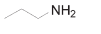
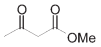
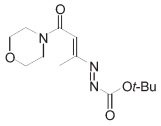
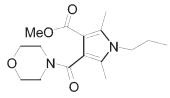
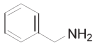
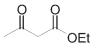
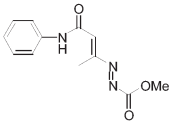
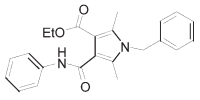
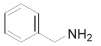
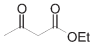
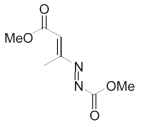
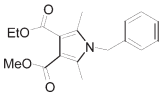
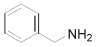
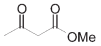
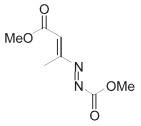
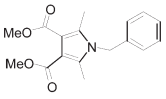
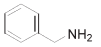
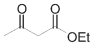
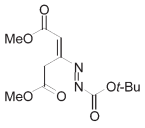
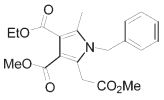
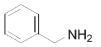
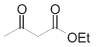
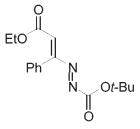
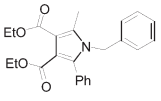
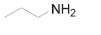
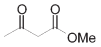
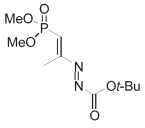
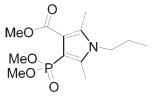
[a] For experimental details, see Supporting Information. [b] Yield of pure isolated products.

reaction (Table 2, entries 1−10). The methyl acetoacetate **2b**, ethyl 3-oxopentanoate **2c**, and allyl acetoacetate **2d** also worked well to give analogous pyrroles **4aba**, **4eca**, and **4cda** (entries 1−3). *N*,*N*-Diethyl-3-oxobutanamide **2e**, 4-morpholin-4-yl-4-oxobutan-2-one **2f**, *N*-(4-methoxyphenyl)-3-oxobutanamide **2g**, and *N*-(4-chlorophenyl)-3-oxobutanamide **2h** furnished the corresponding pyrroles **4dea**, **4dfa**, **4aga**, and **4aha** in good yields (entries 4−7). Interestingly, β-ketothioester **2j** also provides the corresponding pyrrole **4aja** (entry 8). Additionally, pyrroles **4dka** and **4dla** were also obtained with both β-ketosulfone, namely 1-[(4-chlorophenyl)sulfonyl]acetone **2k**, and β-ketophosphones, namely dimethyl acetylmethylphosphonate **2l** (entries 9 and 10), albeit in moderate yields. For these reactions, an appreciable amount of side-products in both enamino compound formation and the aza-heterocyclization

dx.doi.org/10.1021/jo200287k |*J. Org. Chem.* 2011, 76, 2860–2866

Table 3. DDs Scope in the Synthesis of Pyrroles 4[a]



entry			2		4		Yield[b] (%)
1		**1d**		**2e**	 **3b**	 **4deb**	52
2		**1c**		**2b**	 **3c**	 **4cbc**	53
3		**1a**		**2a**	 **3d**	 **4aad**	79
4		**1a**		**2a**	 **3e**	 **4aae**	55
5		**1a**		**2b**	 **3e**	 **4abe**	54
6		**1a**		**2a**	 **3f**	 **4aaf**	47
7		**1a**		**2a**	 **3g**	 **4aag**	34
8		**1c**		**2b**	 **3h**	 **4cbh**	87

[a] For experimental details, see Supporting Information. [b] Yield of pure isolated products.

process were detected. Besides, use of both aliphatic and aromatic 1,3-diketones was unsuccessful, leading to a complicated mixture of products.[22]

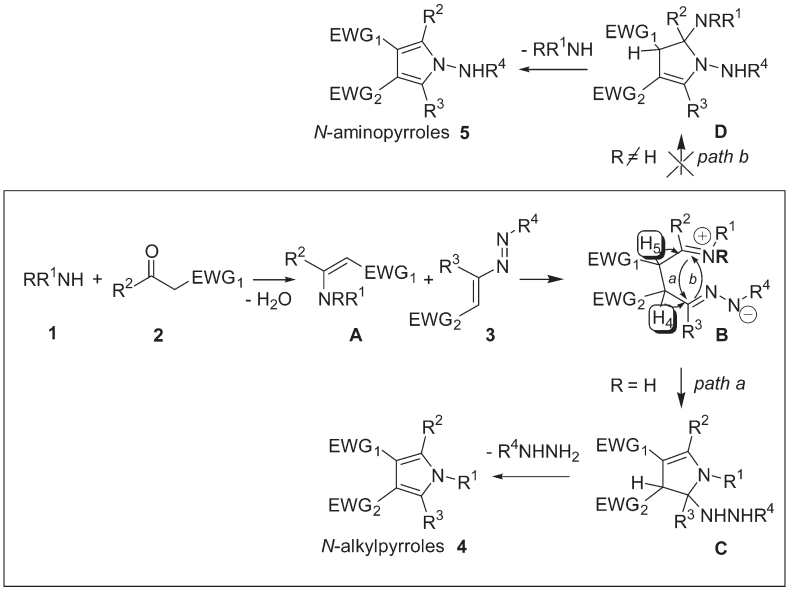
Lastly, the scope of this methodology was further broadened by using several azoene partners. Additional DDs **3b**−**h** differently substituted (Table 3, EWG_2 = COX; X = OMe, OEt, NEt_2, morpholinyl, NHPh; $PO(OMe)_2$; R^2 = Me, Ph, CH_2CO_2Me; R^3 = CO_2Y; Y = Me, *t*-Bu) were compatible with this protocol. A series of 3,4-EWG-substituted pyrroles were so obtained in satisfactory yields (Table 3, entries 1−8).

The structures all of the substituted pyrroles were unambiguously characterized by ^{1}H and ^{13}CNMR, IR, and MS and unequivocally confirmed by comparison of pyrrole-3,4-dicarboxylate **4abe** with the same compound previously reported by Yu et al.[23]

Variations in all three components were accommodated very comfortably in this sequential three-component reaction, generating good to high yields of the functionalized pyrroles. Thus, pyrroles substituted with EWG-containing functional groups at the C-3 and C-4 positions of the heterocyclic ring such as

dx.doi.org/10.1021/jo200287k |*J. Org. Chem.* 2011, 76, 2860–2866

Scheme 2. Mechanistic Rationale for the Synthesis of Pyrrole Derivatives



carboxylic acid derivatives (both symmetrical and unsymmetrical dicarboxylate scaffold) (ester, amide, and/or thioester), sulfone, and phosphonate moiety can be directly obtained. Among them, phosphonylpyrroles could be very interesting compounds because C-phosphorylated heterocycles are known to regulate important biological functions and increase the biological activity, in similar way to that reported for other pharmaceuticals.[24] In addition, it should be noted that the presence of multiple points of derivatization onto the pyrrole skeleton provides opportunity for further synthetic manipulations, for example, to their fused aza-heterocycles.

Although the behavior of DDs with various enamines has been extensively investigated so far, no example of *N*-alkylpyrrole **4** using N-monosubstituted enamines/enaminones are known. In fact, even if a large number of modifications of the enamine reagent have been explored, the studies were restricted to the use of secondary amine-derived enamine.[15a,17b,18] For these reactions, the accepted mechanism of generation of aminopyrrole derivative **5** has been hypothesized to involve as a key step the formation of the zwitterionic transient species of type **B** (Scheme 2).

Based on these results, a plausible mechanism for the sequential three-component reaction was proposed (Scheme 2). In the first step, the formation of enamino ester **A** occurs through condensation of amine **1** with active methylene compound **2**. Next, 1,4-nucleophilic addition of **A** to the azo-ene system of DD **3** produces the nonisolable zwitterionic adduct intermediate **B**, that promptly afforded 5-alkylhydrazino-pyrroline-3-carboxylic acid derivatives **C** by an intramolecular azacyclization via tautomerization CH/NH or 1,3-hydrogen shift. In turn, **C** aromatizes into the *N*-alkylpyrrole **4** by loss of the hydrazine residue (path a, Scheme 2).

The exclusive formation of *N*-alkylpyrrole **4** rather than 1-aminopyrrole **5** may be explained by the light of the nature of the enamine component. In fact, as expected, the use of **A** by introduction of a primary amine has a strong influence on the position of iminium/enamine equilibrium in **B** favoring the intramolecular nucleophilic attack of the NH bond of enamine (derived from 1,3-H5 shift) across the unsaturated C═N bond of a hydrazone function (path a) to give stable aromatic compound **4**. This occurrence would be assisted from the presence of EWG_1 group in the α-position to the iminium functionality (intermediate **B**).

Alternatively, the tautomerization of intermediate **B** via prototropism CH/NH idrazono/hydrazino form (derived from 1,3-H4 shift) before cyclization process (path b, Scheme 2) remains the generally accepted mechanism when simple N,N-disubstituted enamine and DD **3** are used.[15a,17b,18]

Generally, the solvent-free reaction is experimentally simple, proceeds well without any catalyst, and generates virtually no byproducts. In all cases, *N*-alkylpyrrole **4** was obtained as a single product without concurrent formation of *N*-aminopyrrole **5** issued from the alternative pathway. From our study we have revealed that the nature of the amine (hence enamine) component plays a crucial role in aza-annulation reaction. This approach differs from previously reported strategies, as primary enamines were preformed as nucleophiles for heterocycle formation instead of secondary enamines. More precisely, when the N,N-disubstituted enamines were replaced with N-substituted enamines, the desired *N*-alkylpyrroles were obtained with complete reversal of the aza-annulation process. Thus, the chemoselectivity outcome can be modulated simply by tuning the nature of the enaminic components, and EWG substituents at C-3 and C-4 of the pyrrole synthesized can be introduced as well by starting from the appropriately materials **2** and **3**. It is important to note that in the formation of *N*-alkylpyrrole **4**, the nitrogen atom of the heterocycle ring is derived from amine component **1**, and two carbons come from active methylene compound **2**, while the remaining two carbons come from C-3 and C-4 of the DD **3**. Particularly, with respect to the use of secondary enamines, the methodology here described permits an additional, easy diversification of the nitrogen substituents by choosing suitable primary amines.

■ CONCLUSION

In summary, we have reported a novel, efficient, and practical one-pot procedure for the preparation of functionalized pyrroles

dx.doi.org/10.1021/jo200287k |*J. Org. Chem.* 2011, 76, 2860–2866

through a sequential three-component reaction of primary aliphatic amines, active methylene compounds, and DDs. This method circumvents some of the problems and limitations associated with frequently used procedures, is advantageous in terms of simplicity and mildness, and hopefully could find wide application in the synthesis of complex pyrrole-containing compounds. Notably, this environmentally friendly single flask approach avoids transition-metal catalysts, employs readily available materials, and occurs with complete control of pathway selectivity. Current studies to extend this methodology, including the use of other nucleophilic partners, are actively underway.

EXPERIMENTAL SECTION

General Methods. Reagent and solvent purification, work up procedures, and analyses were performed in general as described in Supporting Information.

General Procedure for the Catalyst- and Solvent-free Sequential Three-Component Reaction of Primary Amines ***1****, 1,3-Dicarbonyl Compounds* ***2****, and DDs* ***3****. Synthesis of N-Alkylpyrroles* ***4****.* A mixture of amine **1** (1 mmol) and active methylene compound **2** (1 mmol) was stirred under solvent-free conditions at room temperature for 15 min to 48 h (TLC and ^{1}H NMR monitoring). Then, DD **3**[25] (1 mmol) was added, and the reaction was stirred until the disappearance of the starting materials (over 5−10 min, monitored by TLC). The crude mixture was purified by column chromatography on silica gel to afford the product **4**. Spectroscopic data for representative alkylpyrroles are given below.

*Ethyl 1-Benzyl-4-[(dimethylamino)carbonyl]-2,5-dimethyl-1H-pyrrole-3-carboxylate (****4aaa****).* *N*-Alkylpyrrole **4aaa** was isolated by column chromatography (ethyl acetate) in 65% yield. White waxy; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 1.17 (t, J = 7.2 Hz, 3H), 1.94 (s, 3H), 2.37 (s, 3H), 2.76 (s, 3H), 2.91 (s, 3H), 4.01−4.15 (m, 2H), 5.15 (s, 2H), 6.91 (d, J = 7.2 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 10.0 (q), 10.9 (q), 14.1 (q), 34.0 (q), 37.7 (q), 46.2 (t), 58.8 (t), 108.4 (s), 117.5 (s), 125.6 (d), 127.2 (d), 128.9 (d), 134.9 (s), 137.1 (s), 163.8 (s), 167.1 (s); IR (nujol): ν_{max} = 1701, 1632, 1545, 1262, 1162, 1084 cm^{-1}; MS m/z (%): 328 (M^+) (55), 313 (5), 284 (100), 268 (4), 256 (43), 240 (22), 237 (17), 211 (11). Anal. Calcd for $C_{19}H_{24}N_2O_3$ (328.41): C 69.49, H 7.37, N 8.53. Found: C 69.61, H 7.26, N 8.42.

ASSOCIATED CONTENT

Supporting Information. Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: gianfranco.favi@uniurb.it.

ACKNOWLEDGMENT

This work was supported by the financial assistance from the Ministero dell'Università, dell'Istruzione e della Ricerca (MIUR)—Roma and the Università degli Studi di Urbino "Carlo Bo".

REFERENCES

(1) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reaction in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Ho, T. L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992.

(2) (a) Parson, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163.

(3) For the most recent review, see: (a) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512–1522. (b) Arns, S.; Barriault, L. *Chem. Commun.* **2007**, 2211–2221. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.

(4) For some recent reviews, see: (a) Estévez, V.; Villacampa, M.; Menéndez, C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264–287. (c) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110. (d) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517–531. (e) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043–3060. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603. (g) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783. For examples of pyrroles in natural products, see: (a) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256. (b) Fürstner, A. *Synlett* **1999**, 1523–1533. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119. (d) Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R., Ed.; G. Thieme Verlag: Stuttgart, 1994; Suppl Series E6a, p 556. (e) Gossauer, A. *Die Chemie der Pyrrole*; Springer Verlag: Berlin, 1974. Examples of pyrroles in medicinal chemistry and pharmacology: (a) Lehuédé., J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, *34*, 991–996. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207. Examples of pyrroles in material science: see: (a) Berlin, A.; Vercelli, B.; Zotti, G. *Polym. Rev.* **2008**, *48*, 493–530. (b) Higgins, S. J. *Chem. Soc. Rev.* **1997**, *26*, 247–258. (c) MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27–34.

(5) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476.

(6) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635–1642.

(7) Paal, C. *Chem. Ber.* **1885**, *18*, 367–371.

(8) For recent syntheses, see: (a) Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 4916–4919. (b) Benedetti, E.; Lemiére, G.; Chapellet, L.-L.; Penoni, A.; Palmisano, G.; Malaria, M.; Goddard, J.-P.; Fensterbank, L. *Org. Lett.* **2010**, *12*, 4396–4399. (c) Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094–4097. (d) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. *Org. Lett.* **2010**, *12*, 4066–4069. (e) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N. *Org. Lett.* **2010**, *12*, 2290–2293. (f) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674–1683. (g) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372–374. (h) Fu, X.; Chen, J.; Li, G.; Liu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5500–5504. (i) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16626–16627. (j) Wang, J.-Y.; Wang, X.-P.; Yu, Z.-S.; Yu, W. *Adv. Synth. Catal.* **2009**, *351*, 2063–2066. (k) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005. (l) Cież, D. *Org. Lett.* **2009**, *11*, 4282–4285. (m) Blangetti, M.; Deagostino, A.; Prandi, C.; Tabasso, S.; Venturello, P. *Org. Lett.* **2009**, *11*, 3914–3917. (n) Merkul, E.; Boersch, C.; Frank, W.; Müller, T. J. J. *Org. Lett.* **2009**, *11*, 2269–2272. (o) Ackermann, L.; Sandmann, R.; Kaspar, T. *Org. Lett.* **2009**, *11*, 2031–2034. (p) Fontaine, P.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 1555–1558. (q) Kiren, S.; Hong, X.; Leverett, C. A.; Padwa, A. *Org. Lett.* **2009**, *11*, 1233–1235. (r) Kim, Y.; Kim, J.; Park, S. B. *Org. Lett.* **2009**, *11*, 17–20.

(9) (a) Bhatt, U.; Duffy, B. C.; Guzzo, P. R. *Synth. Commun.* **2007**, *37*, 2793–2806. (b) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811–1813.

(10) Carboxylates provide anchoring points for TiO_2 surfaces with strong binding affinities: Gallopini, E. *Coord. Chem. Rev.* **2004**, *248*, 1283–1297.

(11) Enamine in organocatalysis: (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*,

5606–5655. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(12) Synthesis and structural and pharmacological properties of enamino esters: (a) Salama, N. N.; Eddington, N. D.; Payane, D.; Wilson, T. L.; Scott, K. R. *Curr. Med. Chem.* **2004**, *11*, 2093–2103. (b) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480. (c) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2000**, *122*, 10405–10417. (d) Rappoport, Z. In *The Chemistry of Enamines, Part 1*; Wiley: New York, 1994.

(13) β-Enaminones and related compounds are widely used as versatile intermediates for the synthesis of various nitrogen-containing heterocycles. For reviews, see: (a) Negri, G.; Kascheres, C.; Kascheres, A. J. *J. Heterocycl. Chem.* **2004**, *41*, 461–491. (b) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480. (c) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294. For some recent examples, see:(a) Rueping, M.; Parra, A. *Org. Lett.* **2010**, *12*, 5281–5283. (b) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790–7794. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585–9587. (d) Yan, R.-L.; Luo, J.; Wang, C.-X.; Ma, C.-W.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 5395–5397. (e) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417–2420. (f) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078–8081. (g) Zhu, Q.; Huanfeng, J.; Li, J.; Zhang, M.; Wang, X.; Qi, C. *Tetrahedron* **2009**, *65*, 4604–4613. (h) Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398–8402. (i) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230–7233. (j) Vohra, R. K.; Bruneau, C.; Renaud, J.-L. *Adv. Synth. Catal.* **2006**, *348*, 2571–2574.

(14) For a review on the chemistry of DDs, see: Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109–3127. For recent examples, see:(a) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546–4547. (b) Pitacco, G.; Attanasi, O. A.; De Crescentini, L.; Favi, G.; Felluga, F.; Forzato, C.; Mantellini, F.; Nitti, P.; Valentin, E.; Zangrando, E. *Tetrahedron: Asymmetry* **2010**, *21*, 617–622. (c) Attanasi, O. A.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, G.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468–471. (d) Attanasi, O. A.; Berretta, S.; De Crescentini, L.; Favi, G.; Giorgi, G.; Mantellini, F. *Adv. Synth. Catal.* **2009**, *351*, 715–719. (e) Attanasi, O. A.; Caselli, E.; Davoli, P.; Favi, G.; Mantellini, F.; Ori, C.; Prati, F. *Org. Lett.* **2009**, *11*, 2840–2843. (f) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Behalo, M. S. *Org. Lett.* **2009**, *11*, 2265–2268. (g) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2009**, *11*, 309–312.

(15) (a) Sommer, S. *Angew. Chem.* **1979**, *18*, 695–696. (b) Sommer, S. *Chem. Lett.* **1977**, 583–586.

(16) (a) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem.* **1996**, *61*, 8921–8934. (b) South, M. S.; Jakuboski, T. L. *Tetrahedron Lett.* **1995**, *36*, 5703–5706.

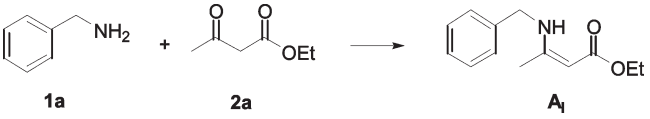
(17) (a) Attanasi, O. A.; Favi, G.; Filippone, P.; Golobič, A.; Perrulli, F. R.; Stanovnik, B.; Svete, J. *Synlett* **2007**, 2971–2974. (b) Attanasi, O. A.; Favi, G.; Filippone, P.; Golobič, A.; Stanovnik, B.; Svete, J. *J. Org. Chem.* **2005**, *70*, 4307–4313.

(18) Rossi, E.; Abbiati, G.; Attanasi, O. A.; Rizzato, S.; Santeusanio, S. *Tetrahedron* **2007**, *63*, 11055–11065.

(19) For some examples of one-pot MCRs for the synthesis of pyrroles involving enaminones, see: (a) Herath, A.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 5182–5185. (b) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674–1683. (c) Liu, W.; Jang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312–315. (d) Alizadeh, A.; Babaki, M.; Zohreh, N. *Tetrahedron* **2009**, *65*, 1704–1707.

(20) A variety of catalysts such as HCl, H_2SO_4, PTSA, AcOH, $HClO_4$, TMSOTf, montmorillonite K10, I_2, $BF_3 \cdot Et_2O$, $InBr_3$, Yb(OTf)$_3$, Bi(TFA)$_3$, Al_2O_3, silica gel, $Zn(ClO_4)_2 \cdot 6H_2O$, $CeCl_3 \cdot 7H_2O$, $FeCl_3 \cdot 6H_2O$, $NaAuCl_4$, CAN, and natural clays have been employed for enamination of β-dicarbonyl compounds. See, for example: Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Adv. Synth. Catal.* **2006**, *348*, 184−190 and references cited herein.

(21) Treatment of benzylamine **1a** with ethyl acetoacetate **2a** at room temperature under solvent-free conditions produced the corresponding enamino ester $\mathbf{A_I}$ in a remarkably clean reaction and in exclusively *Z* form (determined by ^{1}H NMR spectroscopy after 10 min on crude reaction using $CDCl_3$ as solvent, see Supporting Information).



1a **2a** $\mathbf{A_I}$

(22) Aliphatic and aromatic 1,3-dicarbonyl compounds tested include pentane-2,4-dione, 1-benzoylacetone, and cyclohexane-1,3-dione.

(23) Wang, J.-Y.; Wang, X.-P.; Yu, Z.-S.; Yu, W. *Adv. Synth. Catal.* **2009**, *351*, 2063–2066.

(24) Feshchenko, N. G.; Ivonin, S. P.; Tolmachev, A. A.; Pinchuk, A. In *Targets in Heterocyclic Systems-Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2001; Vol. 5, pp 489−520.

(25) DDs **3a**−**h** were synthesized from the corresponding chlorohydrazones by treatment with base (see Supporting Information).