A Novel Ring Transformation of Oxazinones and Azetidinones into Pyrimidinones

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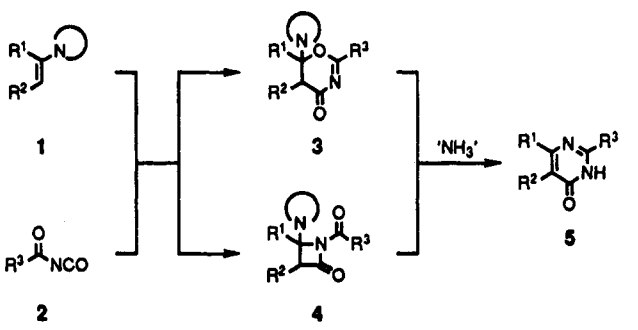
Azetidinones or oxazinones, being easily prepared from enamines and acyl isocyanates, were transformed into highly substituted 4(3*H*)-pyrimidinones upon treatment with ammonium acetate. This novel ring transformation was also accomplished through a one-pot reaction without isolation of the adduct.

Pyrimidines have attracted considerable attention in chemistry[1] and biology.[2] Recently, we disclosed the potent herbicidal activity of 4- and/or 5-substituted 2,5-diarylpyrimidines.[3] A program directed toward further development of new herbicides required a synthesis of highly substituted 4(3*H*)-pyrimidinones, which were the key intermediates to the preparation of the bioactive compounds. Classical approaches to pyrimidine ring systems have generally relied on a variety of condensation reactions to effect the ring closure of appropriate precursors.[4] On the other hand, syntheses of pyrimidines via ring transformation of a variety of heterocycles were well documented.[5]

The utility of heterocumulenes as synthons[6] for various heterocycles prompted us to investigate the behavior of oxazinones **3** and azetidinones **4**, easily prepared from enamines **1** and acyl isocyanates **2**, toward ammonium acetate (Scheme I). As a result, we found new transformation reactions of the labile heterocycles **3** and **4** into highly substituted 4(3*H*)-pyrimidinones **5**. These transformations were also achieved through one-pot reaction without isolation of the resultant adducts **3** and **4** from enamines to afford 4(3*H*)-pyrimidinones **5** in excellent yields.

Scheme I



Results and Discussions

General Reaction Characteristics. The reaction of enamines and various heterocumulenes such as isocyanates or acyl isocyanates has been widely studied, and the scope and limitation of these reactions have been defined.[7] In the case of acyl isocyanates, two kinds of adducts, oxazinones **3** and azetidinones **4**, were formed depending on the sorts of enamines **1** and acyl isocyanates **2** used.[8] By employing typical adducts **3a** and **4a** as starting materials, the transformation reaction into 4(3*H*)-pyrimidinones **5** was examined (Scheme II and Table I).

Via Oxazinone. Oxazinone **3a** was prepared through [$\pi 2 + \pi 4$] cycloaddition from 1-morpholino-1-cyclopentene (**1a**) and benzoyl isocyanate (**2a**) according to the known method.[9] When **3a** was reacted with ammonia or ammonium acetate in MeOH at rt, an acyclic product **6a** was obtained in 64 or 78% yield (entries 1 and 2). The structure of **6a** was determined on the basis of spectroscopic data. The IR absorptions at 3412 or 1687 cm^{-1} and the ^1H-NMR signals of two broad peaks at δ 3.10–3.60 (2 H) and 9.30–9.70 (1 H) suggested the presence of an amino group and amide structure. The elemental analysis and mass spectrum (M^+ m/z 230) of **6a** were in agreement with the assigned structure (see Experimental Section).

Cyclocondensation of **6a** into the condensed pyrimidinones **5a** was achieved by heating in refluxing AcOH or MeOH, **5a** being obtained in a quantitative yield in both solvents (entries 4 and 5). Compound **5a** was identical (mp, IR, and ^1H-NMR) with 2-phenyl-5*H*-6,7-dihydrocyclopenta[*d*]pyrimidin-4(3*H*)-one[10] which was prepared by the reaction of 2-(ethoxycarbonyl)cyclopentanone and benzamidine. The entire sequence from the oxazinone **3a** to the condensed pyrimidinones **5a** could be conveniently done in one pot without isolation of intermediate **6a**, upon treatment with ammonium acetate in refluxing AcOH (entry 6).

On the basis of the results found here, the transformation of **3a** into **5a** is assumed to be a two-step sequence

(1) Brown, D. J.; Mason, S. F. *The Chemistry of Heterocyclic Compounds. The Pyrimidines*; Weissberger, A., Ed.; John Wiley & Sons: New York and London, 1962.
(2) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley; New York, 1980; Vol. 2, p 302.
(3) Kawamura, S.; Sato, J.; Hamada, T.; Sakaki, M.; Sanemitsu, Y. Submitted to *J. Agric. Food Chem.*
(4) (a) Pinner, A. *Chem. Ber.* **1889**, *22*, 1612. (b) Brown, D. J.; Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Chemistry of Heterocyclic Compounds. The Pyrmidines Supplement II*; Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons: New York, Chichester, Brisbane, Toronto, Singapore, 1985; p 21.
(5) van der Plas, H. C. *Ring transformation of Heterocycles*; Blomquist, A. T., Wasserman, H., Eds.; Academic Press: London and New York, 1973.
(6) (a) Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Blomquist, A. T., Ed.; Organic Chemistry, A Series of Monographs; Academic Press: New York and London, 1967; Vol. 9, p 122. (b) Nakayama, Y.; Sanemitsu, Y. *J. Org. Chem.* **1984**, *49*, 1703.
(7) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975; **1982**, *38*, 3363.
(8) Arbuzov, B. A.; Zobova, N. N. *Synthesis* **1974**, 461; **1982**, 433.
(9) Arbuzov, B. A.; Zobova, N. N. Balabanova, F. B. Izv. *Akad. Nauk. SSSR, Ser. Khim.* **1972**, 2086.
(10) Bernáth, G.; Janáky, T.; Göndös, G. Y.; Lázár, J.; Ecsery, Z. *Pharmazie* **1983**, *38*, 270.

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Scheme II

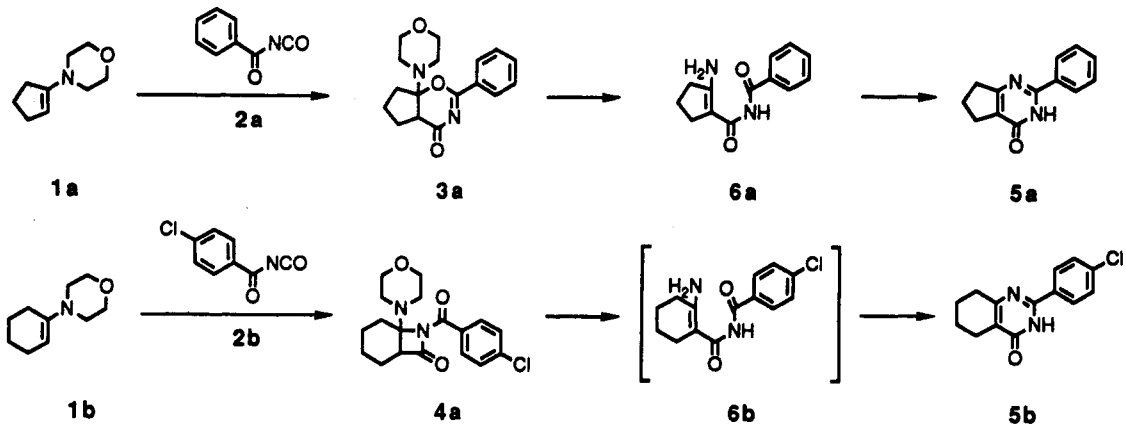


Table I. Synthesis of 4(3*H*)-Pyrimidinones from Oxazinones or Azetidinones

entry	substrates	amines	conditions	products	yield, %
1	3a	$AcONH_4$	MeOH, rt, 10 min	6a	64
2	3a	NH_3	MeOH, rt, 10 min	6a	78
3	6a		MeOH, reflux, 4 h	5a	20
4	6a		MeOH, reflux, 16 h	5a	96
5	6a		AcOH, reflux, 10 min	5a	97
6	3a	$AcONH_4$	AcOH, reflux, 30 min	5a	88
7	4a	$AcONH_4$	MeOH, rt, 1 h	5b	84
8	4a	$AcONH_4$	AcOH, rt, 1 h	5b	84

consisting of the first nucleophilic attack of ammonia toward an oxazinone ring followed by the second cyclocondensation of intermediate **6a**.

Via Azetidinones. The reaction of a labile azetidinone **4a** with ammonium acetate has also been investigated. The starting material **4a** was readily available from cycloaddition of 1-morpholino-1-cyclohexene (**1b**) and 4-chlorobenzoyl isocyanate (**2b**).[11]

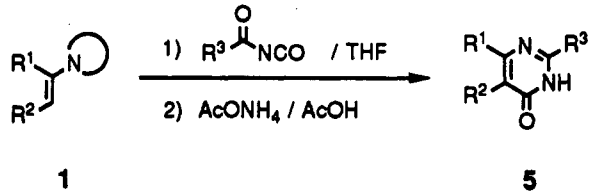
Treatment of azetidinone **4a** with ammonium acetate in AcOH or MeOH at rt for 1 h afforded **5b** as sole product in 84% yield (Table I, entries 7 and 8). The structure of **5b** was identified as 2-(4-chlorophenyl)-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one[10] by comparison of its physical properties with the known condensed pyrimidine **5b**. An attempt to isolate the plausible intermediate **6b** by changing the nature of solvents met with failure. This result reflects the relative ease of cyclization in six-membered ring **6b** rather than in five-membered ring **6a**. The formation of **5b** is assumed to be a two-step reaction, namely the ring opening of azetidinone **4a** by ammonia and cyclocondensation of the resultant intermediate.

Thus, these results clearly illustrated that labile heterocycle species such as oxazinones **3** or azetidinones **4** were smoothly converted into the 4(3*H*)-pyrimidinone ring system, regardless of the type of adduct.

One-Pot Synthesis of Highly Substituted 4(3*H*)-Pyrimidinones. These novel ring transformation reactions encouraged us to extend our methodology to the synthesis of pyrimidinones from enamines in one-pot treatment. So, direct conversion from enamine **1a** to the condensed pyrimidinone **5a** was examined without isolation or purification of the intermediate **3a**. Exposure of benzoyl isocyanate (**2a**) to 1-morpholino-1-cyclopentene (**1a**) in THF at 0 °C for 30 min provided a cycloaddition product **3a** followed by the addition of ammonium acetate in AcOH and subsequent heating to yield **5a** in 93% yield.

(11) Lattrell, R. *Liebigs Ann. Chem.* **1969**, *722*, 142.

Scheme III



Thus, the entire sequence can be smoothly done in a one-pot treatment. In all cases examined, yields of pyrimidinones could be improved by one-pot treatment. Consequently, the majority of transformations described in this paper employ the one-pot synthetic method.

To define the scope of this method, the synthesis of 4(3*H*)-pyrimidinones using various enamines and several acyl isocyanates was investigated (Scheme III). All of the acyl isocyanate species employed in this study were prepared directly from the corresponding amides and oxalyl chloride.[12] Typically, the resultant acyl isocyanates were used without further purification. As shown in Table II, a variety of 4(3*H*)-pyrimidinones were prepared in excellent yields. The structures of the corresponding 4(3*H*)-pyrimidinones **5** were confirmed by ^{1}H-NMR, MS, and IR spectral analyses (Experimental Section). The scope of the process is evident from Table II, which lists several examples of pyrimidinones **5** prepared by this methodology. This novel ring transformation gave pyrimidinones **5** in excellent yields, irrespective of the nature of enamines used (entries 1–3). This demonstrates that the reactivity of enamines appears to have little effect on the transformation reactions. Enamine species with bulky substituents such as **1e** and **1f** provided satisfactory yields of the corresponding pyrimidinones **5h** and **5i**, respectively (entries 10 and 11). These demonstrate the efficacy of the process for the introduction of bulky alkyl groups in the pyrimidinone ring system. In addition, this methodology is particularly suitable for the synthesis of highly substituted pyrimidinones. There has been considerable interest as the key intermediates to prepare the potent herbicidal heterocyclic species in recent paper.[13] The requisite pyrimidinones **5j** and **5k** were prepared in a single step from benzoyl isocyanate (**2a**) and the corresponding enamines **1g** and **1h** that were derived from propiophenone and 2-methoxyacetophenone, respectively (entries 12 and 13).

(12) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1963**, *28*, 1805.
(13) Kawamura, S.; Sato, J.; Hamada, T.; Sakaki, M.; Sanemitsu, Y. *Biosci. Biotech. Biochem.* **1992**, *56*, 1897.

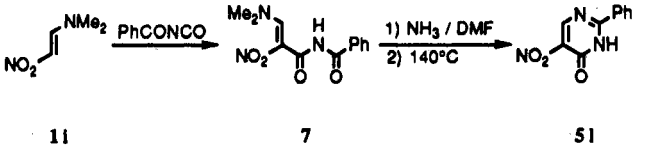
Table II. Synthesis of 4(3*H*)-Pyrimidinones

entry	enamines	acyl isocyanates	products	yields, %
1	1b	2a	5c	93
2	1c	2a	5c	87
3	1d	2a	5c	93
4	1d	2c	5d	85
5	1b	2b	5b	91
6	1d	2d	5e	24
7	1d	2e	5f	20
8	1a	2a	5a	93
9	1a	2f	5g	86
10	1e	2a	5h	83
11	1f	2a	5i	92
12	1g	2a	5j	85
13	1h	2a	5k	85

The reaction of more functionally elaborate enamines with acyl isocyanates has already been investigated.[14] For example, reaction of electron-deficient enamine 1i with benzoyl isocyanate did not give a labile adduct but instead afforded acyclic product 7. Cyclization of 7 occurred upon treatment with ammonia leading to the formation of pyrimidinone 5l[14a] (Scheme IV).

(14) (a) Simchen, G. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 703. (b) Tsuge, O. *Bull. Chem. Soc. Jpn.* **1976**, 2828.

Scheme IV



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Also, the various substitutents on an aryl ring in benzoyl isocyanates had no effect on the overall transformation process (entries 4 and 5). In contrast, the chlorinated acyl isocyanates such as **2d** and **2e** resulted in the poor yields of pyrimidinones **5e** and **5f**, respectively (entries 6 and 7). In these cases, the labile adducts immediately darkened when exposed to ammonium acetate, and no other products were isolated from this reaction.

Summary

This novel ring transformation provides an efficient route to the 4(3*H*)-pyrimidinone ring system. Furthermore, the entire sequence from enamines to pyrimidinones could be done in one pot without isolation of the adducts. Our methodology for the preparation of highly substituted 4(3*H*)-pyrimidinones offers several advantages over existing methods. The starting materials (enamines and acyl isocyanates) can be easily prepared. The reaction is mild and general and gives uniformly high yields. Extension of the present reaction led to the discovery of biologically active pyrimidine species.[13]

Experimental section

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Hitachi 24B (60 MHz) with tetramethylsilane as an internal standard. Microanalytical data were provided by Sumika Analysis Center. Enamines[15] and acyl isocyanates[12] were prepared according to the literature.

Preparation of 2-Amino-1-(*N*-benzoylcarbamoyl)cyclopentene (6a). A mixture of oxazinone **3a** (1.50 g, 5 mmol) and ammonium acetate (1.17 g, 15 mmol) in MeOH (10 mL) was stirred at rt for 10 min. The precipitate was collected and washed with ethanol. Recrystallization from MeOH gave **6a** (0.74 g, 64%) as colorless crystals. Compound **6a** was also prepared using ammonia in MeOH (2 N, 10 mL) in place of ammonium acetate in a similar fashion (yield 0.90 g (78%)): mp 185–187 °C; IR (KBr) 3412, 3291, 1687, 1614 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.45–2.10 (m, 2 H), 2.28–2.76 (m, 4 H), 3.10–3.60 (br, 2 H), 7.25–7.90 (m, 5 H), 9.30–9.70 (br, 1 H); MS *m/z* (relative intensity) 230 (25, M$^+$), 105 (77), 81 (100).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.8; H, 6.1; N, 12.2. Found: C, 68.0; H, 6.2; N, 12.3.

Cyclization of 6a into 5a. A solution of azetizinone **6a** (1.15 g, 5 mmol) in MeOH or AcOH (20 mL) was refluxed for several hours (see Table I). The solution was cooled to rt and then diluted with water (100 mL), and the precipitate was purified directly by recrystallization from ^{i}PrOH to give **5a** as white crystals: mp 242–243 °C (lit.[10] mp 242–244 °C); IR (KBr) 3058, 2894, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90–2.49 (m, 2 H), 2.70–3.20 (m, 4 H), 7.40–7.60 (m, 3 H), 8.00–8.30 (m, 2 H), 12.50–13.00 (bs, 1 H); MS *m/z* (relative intensity) 212 (100, M$^+$).

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7; N, 13.2. Found: C, 73.5; H, 5.7; N, 13.2.

Ring Transformation of 3a (or 4a) into Pyrimidinones 5a (or 5b). A mixture of **3a** (1.50 g, 5 mmol) or **4a** (1.74 g, 5 mmol) and ammonium acetate (1.17 g, 15 mmol) in MeOH or AcOH (20 mL) was stirred (see Table I). The solution was cooled to rt and diluted with water (100 mL), and the resultant precipitate was collected. The product was purified by recrystallization from ^{i}PrOH.

5b: mp 316–318 °C (lit.[10] 318–319 °C); IR (KBr) 3058, 2940, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75–2.30 (m, 4 H), 2.44–3.18 (m, 4 H), 7.69 (d, J = 8 Hz, 2 H), 7.97 (d, J = 8 Hz, 2 H); MS *m/z* (relative intensity) 260 (100, M$^+$), 259 (27).

Anal. Calcd for $C_{14}H_{13}N_2OCl$: C, 64.5; H, 5.0; N, 10.7. Found: C, 64.3; H, 5.0; N, 10.7.

One-Pot Synthesis of Pyrimidinones. Typical Procedure. 2-Phenyl-5*H*-6,7-dihydrocyclopenta[*d*]pyrimidin-4(3*H*)-one (5a). To an ice-cold solution of enamine **1a** (7.65 g, 50 mmol) in dry THF (150 mL) was added dropwise acyl isocyanate **2a** (7.35 g, 50 mmol) diluted with THF (15 mL). The mixture was stirred for 30 min at 0 °C, and then AcOH (150 mL) and ammonium acetate (19.5 g, 0.25 mol) were added. The resulting solution was refluxed for 2 h with continuous removal of THF. The solution was cooled to rt and diluted with water (500 mL), and then the precipitate was collected. Recrystallization from ^{i}PrOH gave 9.86 g (93%) of **5a**.

Compounds **5b–5k** were similarly prepared. Yields, physical, ^{1}H NMR, and analytical data for the compounds are reported as follows.

5b: yield 2.37 g (91%) from **1b** (1.67 g, 10 mmol) and **2b** (1.82 g, 10 mmol).

5c: yield 1.97 g (87%) from **1b** (1.67 g, 10 mmol) and **2a** (1.47 g, 10 mmol); yield 2.10 g (93%) from **1c** (1.65 g, 10 mmol) and **2a** (1.47 g, 10 mmol); yield 1.92 g (85%) from **1d** (1.51 g, 10 mmol) and **2a** (1.47 g, 10 mmol); mp 244–245 °C (from MeOH) (lit.[10] mp 246–247 °C, lit.[16] mp 238–239 °C); IR (KBr) 3070, 2927, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70–1.98 (m, 4 H), 2.50–2.90 (m, 4 H), 7.32–7.70 (m, 3 H), 8.12–8.35 (m, 2 H), 12.8 (bs, 1 H); MS *m/z* (relative intensity) 226 (100, M$^+$), 225 (45).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.3; H, 6.2; N, 12.4. Found: C, 74.0; H, 6.2; N, 12.3.

5d: yield 2.04 g (85%) from **1d** (1.51 g, 10 mmol) and **2c** (1.61 g, 10 mmol); mp 177–178 °C (from ^{i}PrOH); IR (KBr) 3043, 2933, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45–2.04 (m, 4 H), 2.17–2.95 (m, 4 H), 2.43 (s, 3 H), 7.04–7.66 (m, 4 H); MS *m/z* (relative intensity) 240 (100, M$^+$), 239 (96).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.7; N, 11.7. Found: C, 74.9; H, 6.8; N, 11.6.

5e: yield 0.48 g (24%) from **1d** (1.51 g, 10 mmol) and **2d** (1.20 g, 10 mmol); mp 189–191 °C (from ^{i}PrOH); IR (KBr) 3058, 2940, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55–2.10 (m, 4 H), 2.32–2.84 (m, 4 H), 4.43 (s, 2 H); MS *m/z* (relative intensity) 198 (39, M$^+$), 163 (100, M – Cl).

Anal. Calcd for $C_9H_{11}N_2OCl$: C, 54.4; H, 5.6; N, 14.1. Found: C, 54.4; H, 5.5; N, 14.0.

5f: yield 0.53 g (20%) from **1d** (1.51 g, 10 mmol) and **2e** (1.88 g, 10 mmol); mp 220–222 °C (from ^{i}PrOH); IR (KBr) 3058, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70–2.40 (m, 4 H), 2.48–3.42 (m, 4 H), 11.8–12.0 (br s, 1 H); MS *m/z* (relative intensity) 266 (75, M$^+$), 231 (100, M – Cl).

Anal. Calcd for $C_9H_9N_2OCl_3$: C, 40.4; H, 3.4; N, 10.5. Found: C, 40.4; H, 3.4; N, 10.5.

5g: yield 1.65 g (86%) from **1a** (1.53 g, 10 mmol) and **2f** (1.27 g, 10 mmol); mp 184–185 °C (from ^{i}PrOH); IR (KBr) 3012, 2956, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 1.90–2.28 (m, 2 H), 2.61–3.10 (m, 4 H), 11.8–12.2 (bs, 1 H); MS *m/z* (relative intensity) 192 (41, M$^+$), 177 (100, M – CH_3).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.4; N, 14.6. Found: C, 68.7; H, 8.5; N, 14.7.

5h: yield 1.89 g (83%) from **1e** (1.69 g, 10 mmol) and **2a** (1.47 g, 10 mmol); mp 184–185 °C (from MeOH); IR (KBr) 3058, 2940, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 6.44 (s, 1 H), 7.40–7.66 (m, 3 H), 8.20–8.40 (m, 2 H), 13.28 (bs, 1 H); MS *m/z* (relative intensity) 228 (61, M$^+$), 213 (100, M – CH_3).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.1; N, 12.3. Found: C, 73.6; H, 7.0; N, 12.3.

5i: yield 1.97 g (92%) from **1f** (1.53 g, 10 mmol) and **2a** (1.47 g, 10 mmol); mp 183–184 °C (from MeOH); IR (KBr) 3068, 2950,

(15) Haynes, L. W. *Enamines: Synthesis, Structure, and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New York and London, 1969; p 55.

(16) Hünig, S.; Hübner, K. *Chem. Ber.* **1962**, *95*, 937.

1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, J = 6 Hz, 6 H), 2.91–3.30 (m, 1 H), 7.40–7.60 (m, 3 H), 7.45 (s, 1 H), 8.10–8.40 (m, 2 H), 13.2 (bs, 1 H); MS m/z (relative intensity) 214 (71, M^+), 199 (100, M – CH_3).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.6; N, 13.1. Found: C, 72.6; H, 6.6; N, 13.1.

5j: yield 2.23 g (85%) from **1g** (1.87 g, 10 mmol) and **2a** (1.47 g, 10 mmol); mp 253–254 °C (from MeOH) (lit.[17] mp 250 °C); IR (KBr) 3058, 2940, 1662 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 2.23 (s, 3 H), 7.38–8.18 (m, 10 H); MS m/z (relative intensity) 262 (71, M^+), 261 (100).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.6; H, 5.4; N, 10.7. Found: C, 77.6; H, 5.4; N, 10.6.

5k: yield 2.36 g (85%) from **1h** (2.03 g, 10 mmol) and **2a** (1.47 g, 10 mmol); mp 262–263 °C (from MeOH); IR (KBr) 3012, 2894, 1660 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 3.94 (s, 3 H), 7.35–8.15 (m, 10 H); MS m/z (relative intensity) 278 (61, M^+), 104 (100).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found: C, 73.1; H, 5.2; N, 10.0.

(17) Grassi, G.; Foti, F.; Risitano, F. *J. Chem. Res., Synop.* **1983**, 102.