A New [5+1]-Annulation Route to Some Quinazoline and Fused Pyrimidine Derivatives

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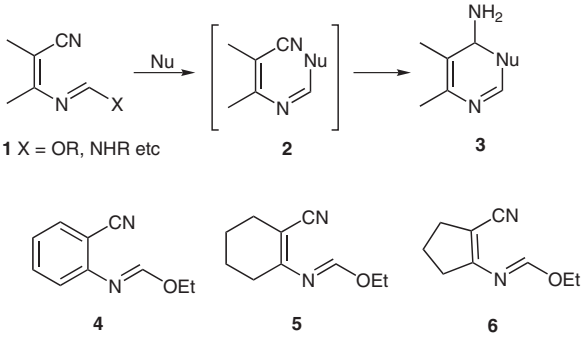
This paper is respectfully dedicated to Professor Alexander McKillop, University of East Anglia, Norwich, UK

Abstract: β-Dicarbonyl compounds, such as diethyl malonate, ethyl acetoacetate and acetyl acetone have been found to add selectively to the iminoether functionality of the 2-ethoxymethyleneaminonitriles leading to a one-pot synthesis of some quinazoline and fused pyrimidine derivatives.

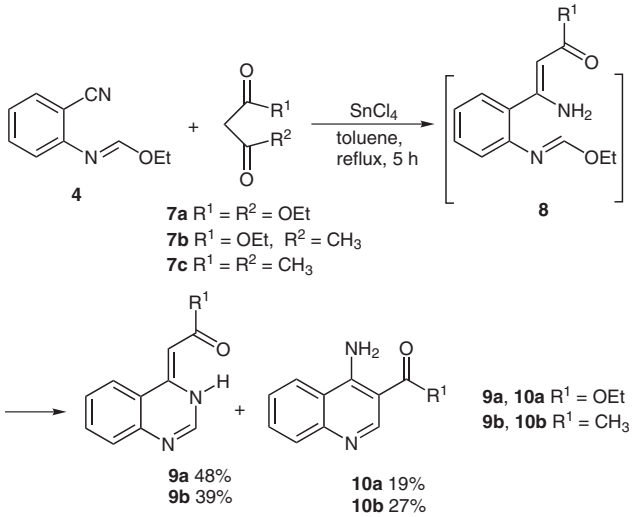
Key words: annulations, heterocycles, nitriles, Lewis acids, tin

Bifunctional iminoethers or amidines represented by the general structure **1** (Scheme 1) have been widely used[1,2] for the synthesis of various nitrogen heterocyclic compounds involving stepwise inter- and intramolecular addition of suitable nucleophilic species. Nucleophiles such as amines, hydrazines, hydrosulfides and hydroxylamines add selectively to the azomethine functionality in **1** to give intermediates which cyclize in an intramolecular fashion to give heterocycles[3–5] (Scheme 1). Carbon nucleophiles such as Grignard reagents or alkyllithiums predominantly act as base towards iminoethers forming isonitriles,[6] but phenylmagnesium bromide has been found to add to 2-amidinonitriles leading to the formation of some quinazoline derivatives.[7] The behavior of other softer carbon nucleophiles towards iminonitriles has largely remained unexplored. Various metal catalysts are known[8,9] to activate carbon–carbon bond formation between the cyano group in nitriles and the inter-carbonylic methylene group of β-dicarbonyl compounds. For the non-electrophilically activated nitriles, stannic chloride has been found[10] to be particularly effective. We were interested to examine whether any selectivity could be observed in the stannic chloride promoted addition of β-dicarbonyl compounds to 2-ethoxymethyleneaminonitriles of the type **4–6** with an aim to develop new routes to some nitrogen heterocyclic systems of interest. Herein, we wish to describe our efforts in this direction.

The starting materials **4–6** were easily prepared by acid catalyzed condensation of the corresponding aminonitriles with triethyl orthoformate as described in the literature.[11]Although these have been occasionally used without isolation, their spectroscopic properties are not reported. A simple procedure for their preparation has thus been developed which allowed their isolation and characterization. When a solution of 2-ethoxymethyleneaminobenzonitrile (**4**), diethyl malonate and stannic chloride in the molar ratio of 1:1:2 was refluxed in toluene for five hours, an orange colored solid separated. This presumable tin complex on treatment with saturated sodium carbonate solution liberated two products after chromatography which were characterized to be the quinazoline derivative **9a** (48%) and the quinoline derivative **10a** (19%) (Scheme 2). The formation of these products could be explained if it is assumed that a selective addition of diethyl malonate to the nitrile group in **4** has taken place to form an intermediate of the type **8** (not isolated) which then cyclizes through two different possible modes involving the ambident nucleophilic centers within the enamine moiety.



Scheme 1



Scheme 2

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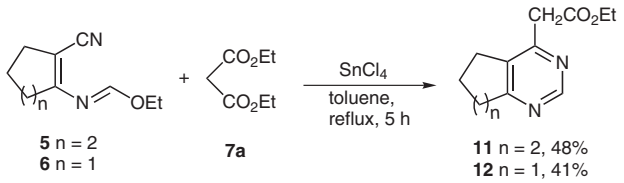
It is interesting to note that when the reaction was conducted under identical conditions but using ethyl acetoacetate as the dicarbonyl compound, the same mixture of products **9a** (42%) and **10a** (21%) was formed. Reaction of **4** with acetylacetone analogously led to the formation of **9b** (39%) and **10b** (27%). Apparently, one of the carbonyl groups was lost during all of these reactions. Although it is difficult to predict exactly at which stage the acyl group is lost, this kind of deacylation[12] has been previously noted in related reactions. Moreover, the products **9a**,**b** were obtained in geometrically pure form. We have tentatively assigned *Z*-configuration to these as an intramolecular hydrogen bond between the NH proton and the carbonyl group is expected to contribute to their stability. Formation of the dihydroquinazolines **9a**,**b** and the aminoquinoline derivatives **10a**,**b** was a pleasing outcome since various quinazoline and quinoline derivatives are known to have interesting biological properties.[13]

The iminonitrile **5**, prepared from 1-amino-2-cyanocyclohexene, was then reacted with diethyl malonate under the conditions developed previously. The only isolable product from this reaction was characterized from spectroscopic and analytical data to be the tetrahydroquinazoline derivative **11** (Scheme 3). The same product also formed from the reaction of **5** with ethyl acetoacetate but a slight drop in the yield (40%) was noticed. The iminonitrile **6**, prepared from 1-amino-2-cyanocyclopentene, also behaved similarly. Thus, the reaction of the latter with diethyl malonate under identical conditions led to the formation of the pyrimidine derivative **12** as the only isolable product (41%).



Scheme 3

In short, we have demonstrated that the stannic chloride promoted reaction of β-dicarbonyl compounds with 2-ethoxymethyleneaminonitriles **4**–**6** led to the formation of some important heterocyclic compounds like quinazoline,[14] pyrimidine and quinoline derivatives. Although the yields are moderate, the developed [5+1]-annulation procedure provides direct access to some of these important heterocyclic ring systems in one step, which may prove to be of utility.

Melting points were determined in open capillaries and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrometer in $CDCl_3$ or DMSO-d_6 and referenced to the solvent signal. Low-resolution mass spectra were recorded on a Jeol-JMS 600 instrument at an ionizing potential of 70 eV. Microanalyses were performed on a Perkin-Elmer 204B elemental analyzer. Petroleum ether refers to the fraction boiling in the range of 60–80 °C. Silica gel used was purchased from Spectrochem, India Limited. 1-Amino-2-cyanocyclohexene[15] and 1-amino-2-cyanocyclopentene[16] were prepared following literature procedure.

2-Ethoxymethyleneaminonitriles 4-6; General Procedure

A solution of the appropriate 2-aminonitrile (0.1 mol) in triethyl orthoformate (103.7 g, 0.7 mol) was heated under reflux in a flask fitted with a 15 cm long Vigreux column until the distillation of EtOH ceased (ca. 1–2 h). The mixture was cooled, and a few crystals of *p*-TsOH acid were added. The mixture was refluxed again until no more EtOH was collected (ca. 1 h). Excess solvent was then distilled off under reduced pressure and the remaining material was purified by distillation under high vacuum.

Ethyl *N*-2-Cyanophenylformimidate (4)

Yield: 82%; bp 112 °C/0.5 mm.

IR (neat): 2225, 1640, 1590, 1215 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80–7.85 (m, 5 H), 4.42 (q, 2 H, *J* = 7.5 Hz), 1.42 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 151.1, 133.6, 133.0, 124.3, 120.8, 117.3, 107.2, 62.2, 14.0.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.82; H, 5.68; N, 16.13.

Ethyl *N*-2-Cyanocyclohex-1-enylformimidate (5)

Yield: 86%; bp 110 °C/0.2 mm.

IR (neat): 2230, 1650, 1635, 1595 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1 H), 4.43 (q, 2 H, *J* = 7.5 Hz), 2.32 (br s, 4 H), 1.67–1.61 (m, 4 H), 1.32 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 154.6, 119.2, 95.9, 62.8, 29.0, 26.5, 21.7, 21.6, 14.0.

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.28; H, 7.99; N, 15.65.

Ethyl *N*-2-Cyanocyclopent-1-enylformimidate (6)

Yield: 86%; mp 44 °C (toluene).

IR (KBr): 2210, 1630, 1615, 1230 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1 H), 4.36 (q, 2 H, *J* = 7.5 Hz), 2.40–2.20 (m, 4 H), 2.10–1.95 (m, 2 H), 1.36 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 157.5, 117.0, 98.3, 63.3, 32.7, 31.8, 21.8, 14.1.

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.95; H, 7.22; N, 17.14.

Reaction of 2-Ethoxymethyleneaminonitriles 4–6 with β-Dicarbonyl Compounds; General Procedure

$SnCl_2$ (1.2 mL, 10 mmol) was added dropwise to a stirred solution of the appropriate 2-ethoxymethyleneaminonitrile **4**–**6** (5 mmol) and the β-dicarbonyl compound (5 mmol) in anhyd toluene (15 mL) at r.t. under N_2. The mixture was refluxed for 5 h by which time an orange mass separated. It was then allowed to come to r.t., and excess toluene was distilled off in vacuo. The residual mass was stirred with aq sat. Na_2CO_3 solution (40 mL) and then extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed successively with H_2O (2 × 40 mL), brine (20 mL), and then dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave a crude product, which was chromatographed on silica gel using an appropriate eluent.

Ethyl (*Z*)-2-[Quinazolin-4(3*H*)-ylidene]acetate (9a)
Eluent for chromatography: 30% EtOAc in petroleum ether. Removal of the solvent afforded the product as a colorless solid; yield: 48%; mp 104 °C (EtOAc–petroleum ether) (Lit.[17] mp 103 °C); R_f 0.55.

IR (KBr): 3200, 2800, 1650, 1620 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.34 (br s, 1 H), 7.80 (d, 1 H, *J* = 3 Hz), 7.72 (d, 1 H, *J* = 8.9 Hz), 7.61–7.52 (m, 2 H), 7.37–7.28 (m, 1 H), 5.49 (s, 1 H), 4.21 (q, 2 H, *J* = 6.9 Hz), 1.33 (t, 3 H, *J* = 6.9 Hz).

MS (EI): *m*/*z* (%) = 216 (M^+, 59), 170 (79), 144 (100).

Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.95. Found: C, 66.83; H, 5.91; N, 12.68.

Further elution with the same solvent provided the known[18] ethyl 4-aminoquinoline-3-carboxylate (**10a**) as a colorless solid.

10a
Yield: 19%; mp 200 °C (EtOH); R_f 0.21.

IR (KBr): 3350, 2980, 1680, 1640, 1590 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.91 (s, 1 H), 8.37 (d, 1 H, *J* = 8.4 Hz), 8.30 (br s, 2 H), 7.80 (t, 1 H, *J* = 8.5 Hz), 7.74 (dt, 1 H, *J* = 6.9, 1.2 Hz), 7.52 (dt, 1 H, *J* = 7.2, 1.2 Hz), 4.34 (q, 2 H, *J* = 6.9 Hz), 1.36 (t, 3 H, *J* = 6.9 Hz).

MS (EI): *m*/*z* (%) = 217 (M^+ + 1, 100), 188 (12), 171 (55).

Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.95. Found: C, 66.72; H, 5.32; N, 12.94.

(*Z*)-1-[Quinazolin-4(3*H*)-ylidene]propan-2-one (9b)
Eluent for chromatogarphy: 30% EtOAc in petroleum ether. Removal of the solvent afforded the product as a colorless solid; yield: 39%; mp 111 °C (EtOAc–petroleum ether) (Lit.[17] mp 109 °C); R_f 0.61.

IR (KBr): 3100, 1630, 1614, 1590, 1550, 1480 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 14.52 (br s, 1 H), 7.98 (d, 1 H, *J* = 2.4 Hz), 7.84 (d, 1 H, *J* = 8.1 Hz), 7.77–7.62 (m, 2 H), 7.45–7.40 (m, 1 H), 6.02 (s, 1 H), 2.26 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9 (s), 149.7 (s), 145.5 (s), 142.5 (d), 133.4 (d), 128.2 (d), 127.3 (d), 123.2 (d), 119.5 (s), 89.3 (d), 29.7 (q).

MS (EI): *m*/*z* (%) = 186 (M^+, 89), 171 (100), 143 (42).

Anal. Calcd for $C_{11}H_{10}N_2O$ (186.21): C, 70.95; H, 5.41; N, 15.04. Found: C, 71.23; H, 5.46; N, 15.29.

Further elution with the same solvent provided the known[18] 1-(4-aminoquinolin-3-yl)ethanone (**10b**) as a colorless solid; yield: 27%; mp 220 °C (EtOH); R_f 0.24.

10b
IR (KBr): 3440, 3340, 3230, 1640, 1585, 1550 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.99 (s, 1 H), 8.28 (d, 1 H, *J* = 8.1 Hz), 7.86 (br s, 2 H), 7.63–7.55 (m, 1 H), 7.47 (t, 1 H, *J* = 7.5 Hz), 7.21 (t, 1 H, *J* = 7.2 Hz), 2.49 (s, 3 H).

Anal. Calcd for $C_{11}H_{10}N_2O$ (186.21): C, 70.95; H, 5.41; N, 15.04. Found: C, 71.29; H, 5.76; N, 15.30.

Ethyl 2-(5,6,7, 8-Tetrahydroquinazolin-4-yl)acetate (11)
Eluent for chromatography: petroleum ether–EtOAc (3:1). Removal of the solvent afforded the product as a viscous liquid; yield: 48%.

IR (neat): 2938, 1737, 1615, 1567, 1388, 1267, 1179 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.86 (s, 1 H), 4.20 (q, 2 H, *J* = 7.2 Hz), 3.78 (s, 2 H), 2.90–2.78 (m, 2 H), 2.72–2.61 (m, 2 H), 1.87 (br s, 4 H), 1.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3 (s), 166.0 (s), 161.1 (s), 155.4 (d), 129.1 (s), 61.3 (t), 40.9 (t), 32.3 (t), 24.7 (t), 22.3 (t), 22.0 (t), 14.1 (q).

MS (EI): *m*/*z* (%) = 220 (M^+, 48).

Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.32; H, 7.53; N, 12.71.

Ethyl 2-(6,7-Dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)acetate (12)
Eluent for chromatography: 30% EtOAc in petroleum ether. Removal of the solvent afforded the product as a viscous liquid; yield: 41%.

IR (neat): 2979, 1738, 1585, 1561, 1386 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 4.20 (q, 2 H, *J* = 7.2 Hz), 3.77 (s, 2 H), 3.07–2.94 (m, 4 H), 2.16 (m, 2 H), 1.27 (t, 3 H, *J* = 7.1 Hz)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (s), 168.0 (s), 164.2 (s), 155.6 (d), 134.5 (s), 61.6 (t), 39.6 (t), 34.2 (t), 25.7 (t), 24.2 (t), 14.2 (q).

MS (EI): *m*/*z* (%) = 206 (M^+, 86), 161 (26), 132 (100).

Anal. Calcd for $C_{11}H_{14}N_2O_2$ (206.24): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.23; H, 7.11; N, 13.66.

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References

(1) Taylor, E. C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles*; Wiley-Interscienec: New York, **1970**.
(2) Nelson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: New York, **1975**, 451–459.
(3) Younes, M. I.; Metwally, S. A. M.; Atta, A. H. *Synthesis* **1990**, 704.
(4) Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. *Tetrahedron Lett.* **1984**, *25*, 4813.
(5) Gewald, K.; Schäfer, H.; Bellmann, P.; Müller, H. *Chem. Ber.* **1991**, *124*, 1237.
(6) (a) Strekowski, L.; Wydra, R. L.; Cegla, M. T.; Czarny, A.; Harden, D. B.; Patterson, S. E.; Battiste, M. A.; Coxon, J. M. *J. Org. Chem.* **1990**, *55*, 4777. (b) Strekowski, L.; Cegla, M. T.; Harden, D. B.; Mokrosz, J. L.; Mokrosz, M. J. *Tetrahedron Lett.* **1988**, *29*, 4265.
(7) Bergman, J.; Brynolf, A.; Elman, B.; Vuorinen, E. *Tetrahedron* **1986**, *42*, 3697.
(8) Basato, M.; Corain, B.; Marcomini, A.; Valle, G.; Zanotti, G. *J. Chem. Soc., Perkin Trans. 2* **1984**, 965.
(9) Corain, B.; Crotti, C.; Del Pra, A.; Filira, F.; Zanotti, G. *Inorg. Chem.* **1981**, *20*, 2044.
(10) (a) Veronese, A. C.; Callegara, R.; Ali Salah, S. A. *Tetrahedron Lett.* **1990**, *31*, 3485. (b) Campbell, J. B.; Firor, J. W. *J. Org. Chem.* **1995**, *60*, 5243. (c) Scavo, F.; Helquist, P. *Tetrahedron Lett.* **1985**, *26*, 2603. (d) Singh, B.; Lesher, G. Y. *Synthesis* **1978**, 829.
(11) (a) Taylor, E. C.; McKillop, A.; Veromen, S. *Tetrahedron* **1967**, *23*, 885. (b) Goldman, L.; Marsico, J. W.; Gazzola, A. L. *J. Org. Chem.* **1956**, *21*, 599.

(12) Veronese, A. C.; Gandolfi, V.; Basato, M.; Corain, B. *J. Chem. Res., Synop.* **1988**, 246.
(13) (a) Jhone, S. In *Progress in Drug Research*, Vol. 26; Jucker, E., Ed.; Birkhäuser Verlag: Basel, **1982**, 259–341. (b) Boschelli, D. H. *Drugs Future* **1999**, *24*, 515.
(14) For some recent reports on the synthesis of quinazoline derivatives, see: (a) Bathini, Y.; Sidhu, I.; Singh, R.; Micetich, R. G.; Toogood, P. L. *Tetrahedron Lett.* **2002**, *43*, 3295. (b) Vilalgordo, J. M.; Obrecht, D.; Chucholowsky, A. *Synlett* **1998**, 1405. (c) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235. (d) Nemes, P.; Balazs, B.; Toth, G.; Scheiber, P. *Synlett* **2000**, 1327. (e) Xue, S.; McKenna, J.; Shieh, W.-C.; Repic, O. *J. Org. Chem.* **2004**, *69*, 6474.
(15) Williams, J. K. *J. Org. Chem.* **1963**, *28*, 1054.
(16) Thompson, Q. E. *J. Am. Chem. Soc.* **1958**, *80*, 5483.
(17) Singh, H.; Narula, S. S.; Gandhi, C. S. *Tetrahedron Lett.* **1977**, 3747.
(18) Marecki, P. E.; Bambury, R. E. *J. Pharm. Sci.* **1984**, *73*, 1141.